

TINNITUS TALK  
— PODCAST —  
EPISODE 12



FREQUENCY THERAPEUTICS  
Hearing Lost and Found

00:00 General introduction

Carl LeBel: “To be part of something that no one has done before is sort of a rare opportunity in a career and we take that opportunity and responsibility very seriously.”

**Hazel:** Do you know what the single most active thread on the Tinnitus Talk forum is about? Well, it’s about the company that is featured in this very episode.

I’m Hazel and you’re listening to the Tinnitus Talk podcast. Our previous episode was a very positive and exciting interview with **Thanos Tzounopoulos**, who’s working on a drug to quieten tinnitus, I’d highly recommend you listen to it if you haven’t already done so. And today is another episode on hearing regeneration.

The company we spoke to, **Frequency Therapeutics**, is perhaps closer than anyone to getting a drug to market that promises to restore some of our lost hearing. We spoke with the Chief Development Officer of the company, **Carl LeBel**. He explained how their drug FX-322, currently under development, is meant to work and what results they’ve seen so far.

It is quite a technical episode. Because we had the pleasure of speaking with an executive of the company, these are busy people and so we really only had one hour to interview him. That meant we didn’t have time to ask a lot of clarification questions or repeat certain parts. For that reason, we chose to do a little inhouse debrief, which you will hear after the main interview, where we try to explain some of the more technical concepts in simple terms. So, if you get confused at any point, hopefully the debrief will help you out.

I had some help doing this interview. I felt a little bit out of my depth with the technical nature of the topic, and at the same time we have a strong contingent of Tinnitus Talk forum members who follow Frequency very closely and know a lot more about the topic than myself. So, we invited two of those members to help us out. You will hear Jackson, aka **mrbrightside614** on the forum, as my co-interviewer and **FGG** who during the debrief will explain some of the technical concepts to you.

I want to thank Frequency Therapeutics for being so forthcoming in arranging this talk, in particular **Suzanne Day**, with whom we must have exchanged dozens of emails, and of course Carl himself. And now, without further ado, let's listen to Carl LeBel.

## 02:32 Introducing Carl LeBel, Chief Development Officer, Frequency Therapeutics

**Hazel:** Hey everyone, welcome to the **Tinnitus Talk Podcast**. I'm very pleased to be joined here today by **Carl LeBel**, he is the **Chief Development Officer of Frequency Therapeutics**. Welcome, Carl.

**Carl:** Thank you Hazel. It's great to be here with you and the listeners.

**Hazel:** And we are also joined by **Jackson Jones**, Jackson is an esteemed member of the Tinnitus Talk online community, who – I would say – very avidly follows all the developments around Frequency Therapeutics, welcome Jackson.

**Jackson:** Thank you, yes. We are very happy to have you on here.

**Carl:** Our pleasure.

**Hazel:** Yeah, so Carl, I'm not sure if you are aware, but the Tinnitus Talk community has for years actually been following Frequency Therapeutics very closely. We have a thread on the forum which has I think 9000 posts and nearly a million views. So it is one of our most active threads. I'm not sure if you are aware that you are being followed that closely by the tinnitus community.

**Carl:** It's great to hear, I think, we are aware that activity in the area is certainly picking up along with the interest in this. Like us and others to be able to advance these programmes, you know, through development, I think that's just gonna get even greater.

**Hazel:** Yeah, so we have a lot of people who are very anxious to hear from you guys and get more detail on FX-322. We got a lot of requests to have you on the podcast, so we are very grateful that you are able to spare some time for us. Carl, maybe you could just start by giving our listeners a general introduction to Frequency Therapeutics and yourself as well, what is your background and how did you first get interested in this kind of work?

## 04:16 Beginnings of Frequency and FX-322

**Carl:** I'm happy to. So, Frequency was founded in 2014, and it was based on technology that was jointly developed in the labs of **Dr Bob Langer at MIT** and **Dr Jeff Karp at Harvard**. And they were interested in understanding what are the signals that are involved in regenerative tissues, and in particular highly regenerative tissues. So their first focus was in the small intestines, which is very active. The lining of our small intestines turns over roughly every 4 to 5 days. So it is one of the more highly regenerative and restorative tissues that we have. And when they began to look at the signals that were involved in the tissue being able to do that, they identified that there were stem-like cells, these are called LGR5-positive cells, in the small

intestines. And those cells are very active, and they are dividing and replicating, and that was what enabled the tissue to turn over so rapidly.

Well, as part of their work, they uncovered the fact that those same cells are actually present in the cochlea, kind of like close cousins of those cells, but the signals are not there. And so those cells are essentially quiescent, they are quiet, they provide some support, but they don't do the work of what they were initially designed to do, which is to form sensory hair cells. And so that really formed the foundation of Frequency, and since then we have been working on understanding those signals and then trying to create a drug that can turn those cells on to make new sensory hair cells. So that's sort of a background to Frequency.

## 06:10 Carl's professional background

**Carl:** And I am a drug developer by training, I've been in the biotech-industry for about 30 years or so and spent the bulk of my career at a company in the West Coast, well based on the West Coast, called **Amgen**. And that's where where I really learned how to really develop drugs, I learned about clinical development and got an opportunity to work in a number of different disease settings. So Amgen was formed on the basis of recombinant proteins, like erythropoietin, and so they started treating conditions like anaemia, neutropenia, which is a loss of white blood cells. And then I got involved in diabetes and various cancer indications.

So, that's where I learned the trade, if you will, and it really is a trade, understanding how to sort through this labyrinth of drug development, work with health authorities around the world. And in the late 2000s, I decided to leave Amgen. I was looking for a smaller company. And I got involved in the ear, a colleague of mine connected me to a company in San Diego, and they asked me to join as their Chief Scientific Officer in that company. It was called **Otonomy**, and they're still working in the ear, looking at balance disorders, and they're looking at hearing loss as well. So I spent 8 years, 7 – 8 years there, and really learned a lot about the ear, a lot about the conditions of the ear, and how to do clinical trials in this space. And so I was able to get a drug approved for ear infections, for children that were getting tympanostomy tubes.

And then I decided, it feels like it's time to retire, so I relocated from the West Coast to the North-East. And I wasn't looking to come back to work. I wanted to spend my time with my grand-son, kayaking, and just kind of hang out with the family. But I wanted to keep my brain a little bit sharp, and so Bob Langer, of all people, one of the co-founders, connected me to **David Lucchino**, who is the **CEO of Frequency**. And David invited me to come by and just chat, just talk about our common interest in the area. And he asked me if I were willing to consult for them, and in particular he wanted me to review the documents they were going to send to FDA to support the IND. And I said: "Great, that sounds like a wonderful idea." And I looked at those documents and read the data. A lot of this is proprietary. And once I saw that, I said to myself: "Oh dear, I think I made a mistake retiring." I had to come out of retirement, and then I joined Frequency full-time about 2,5 years ago. And we're just on the cusp of something truly remarkable, we think.

**Hazel:** Wow, so it sounds like it was a good decision to come back and has worked well for both you and the company.

**Carl:** Certainly. To be part of something that no-one has done before us is something of a rare opportunity in a career. And we take that opportunity and that responsibility very seriously. We are unified as a team to try to advance this programme forward as fast as we possibly can.

## 09:35 Professional interest in hearing

**Hazel:** What is it that fascinates you so much about hearing in particular?

**Carl:** Well, I think one doesn't have to look to far to know somebody that has some level of hearing dysfunction. My mother has bilateral hearing aids. She had said to me once, I think she was still in her 70s, early 70s, and she said – I noticed that she was having a harder time hearing, and I said: "Mom, what do you think about maybe going to get you a hearing test?" And then she said, she wanted to take care of her eyes first. And then, once she got her eyes taken care of, she would go and take care of her ears. And the first day they fitted her hearing aids, there was a huge difference. She was reconnected with us, she didn't feel isolated. And that struck me. And I thought that that is probably more common than my own experience. And I think it's fairly common if you look at individuals that have a loss of hearing function. We think that concept of hearing health is tremendously important, and there is a number of ways, and we want to help with that. And obviously we are focused on hearing therapeutic. But we are strong supporters, and we think this is just a huge unmet medical need, and we're glad kind of where we are right now, but want to go fast.

**Hazel:** And where does tinnitus factor into all of this? Is that something that you later sort of came to realise as an important part of the equation, or was it there from the beginning, that realisation?

**Carl:** It has always been a question mark for us. Tinnitus is a difficult – you all know it is difficult to diagnose and it is difficult to compare what one person's level of tinnitus is versus another. But to us it would not be surprising to have an association with a loss of hearing function. And it's a common complaint that many people have hearing loss, they have to deal with. And so we have imagined that it could be possible that – you know our therapeutic of FX-322 is designed to restore these sensory hair cells. We know the function of these hair cells, they amplify, no. 1. But more importantly, we think, they tune and they filter sound. And that tuning and filtering is really what can help one with the clarity of information, and particularly the clarity of language and words, but this tuning and filtering can sort of take out background noise or background signals that one might be perceiving. So it's entirely possible this could also end up being beneficial for tinnitus as well. We don't have any data on this yet, but it certainly wouldn't surprise us, if there was a potential benefit.

**Hazel:** So, let's talk a bit about your drug under development for hearing regeneration, FX-322. So, I'll just kick off with a very general question, and then Jackson, feel free to jump in with more in-depth follow-up question.

## 12:52 The discovery of FX-322

**Hazel:** So, Carl, can you start by just providing a general introduction to **FX-322**, how was it discovered, and what does it do?

**Carl:** Yeah, that's a really great question and an important one to understand. So I mentioned my background in drug development. So, often times companies when they're developing drugs, they'll start with one molecule, it's just easier to test one molecule, understand its dose, understand what's the route and the schedule that one needs to give it by. But this was one of the things that struck me when I first looked at the frequency data. I didn't appreciate this, but FX-322 is really comprised of two molecules, and these two molecules are going after two of these pathways that control the progenitor cells in the cochlea. One can't – we believe – one can't just use one drug to treat, we believe it has to be more than one drug.

And it makes sense to us, biologically, because if one thinks about what these cells are doing, when we are in the third trimester of our mothers' wombs, that's when our hair cells are developing. And these progenitor cells, or these stem cells, are really active during that period. And these signals that I'm talking about are on, they are constantly on, telling those stem cells to make more sensory hair cells, make outer hair cells, make inner hair cells, make sure that the neuro-circuitry is connected. There are all those genes that are turned on at that point. But the moment we are born, those shut down. Those signals stop. And so this was the discovery, as I mentioned in the beginning, in the small intestine, now applied to the cochlea, and when you bring those signals back, those cells get activated.

And so it requires these two small molecules to do it – we combine them into a formulation, we deliver it locally to the ears, so our administration has to be given by an **Otolaryngologist** or Ear-Nose-Throat specialist. The intertympanic injection, as it's called, is a fairly straightforward procedure. You can do it in an office-based setting, under a little bit of topical anaesthetic applied to the ear drum. The ENT will bring a needle down the external canal, poke a small hole through the ear drum and apply our material. And that really takes only a few seconds to inject it. And once done, the individuals can sit up and be on their way.

So the administration itself is a fairly straightforward procedure, but we think it's important since getting drugs to the ear is not an easy thing to do. You can't take a pill and have a therapeutic get to the ear, it's just not selective enough, it's a protected space in the body, you can't get drug concentrations high enough, so this local procedure that we use, where we formulate our two drugs into a polymer – and here's one of the tricks that we use – that polymer turns to a gel once you have injected it in the middle ear, okay. And when that gelation occurs, that gives us enough residence time in the middle ear for our drugs to diffuse into the cochlea. And we've established that through a number of pre-clinical efforts that we've looked at. So again, our belief is, you have to use more than one molecule. We believe that these two molecules do something very special that we've been able to establish in our preclinical programme, and now for the first time we've identified this hearing – what we're calling a hearing restoration signal – in humans that have really chronic hearing loss.

**Hazel:** Jackson, I'm sure this raises more questions for you, feel free.

**Jackson:** Yeah. I actually was gonna touch on a couple of those things later on with some of the questions. We are very excited that we're getting a local delivery of the drug. We have long thought on the tinnitus podcast, usually, when somebody gets down with tinnitus, they really only have a few crucial hours to respond to it, maybe up to 48, where, you know, you either get a high dose of oral prednisone to mediate the inflammation, or you get – if you have some really competent medical practitioners, you get an intertympanic dexamethasone

injection, and that can sometime mitigate whatever tinnitus may be of consequence after, the hearing trauma or what have you. So we're very – that's part of the reason why I'm excited about FX-322, that it's a local delivery. There are some issues with systemic delivery in terms of circulating to the ear, as you pointed to. But yeah, that's just a point of definitely emphasis and optimism for me.

## 18:11 Misconceptions around steroid use

**Carl:** It's interesting that you – you know the whole concept of use of **steroids**, they've never been shown to work, there's never really been a prospective, well-controlled, randomised, placebo-controlled, double-blinded clinical trial done with steroids, where you're taking individuals that perhaps they're going to experience sudden hearing loss. Or they're having some sort of an acoustic trauma and then they have tinnitus that comes along with that. No-one has conducted a trial as I described, to really show that they work. And so today, it's frontline therapy, it's all off-label, but there's nothing else. And so they don't believe that steroids will do any harm, so they deliver them and they cross their fingers. And everyone uses a different protocol, there's no standardisation of the dose of the steroids. The steroid itself, they use **methopredisalone**, they use **dexamethasone**. How often do you give it, how much do you give? These are just question marks. And so, you know, again, we're taking a classical drug development approach here, but in the ear.

## 19:24 How does FX-322 get delivered?

**Carl:** You know, we really feel strongly about these fundamental principles of when you're trying to develop a drug to determine: Does my drug get there? That's the most basic question. And if it does get there, how much of it gets there, right? And lastly, if you know you can get a drug there and you know you can get enough there, then does it do something? So here, I look at those three, you know, basic questions, about whether one can advance a drug therapeutic. And I think we have ticked all three of those boxes.

And so – and I bring that up just because I want to emphasise a couple of recent bits of data that we have disclosed. And so this first question about, does it get there? Measuring drug levels in the cochlea is really hard to do, right? The only instance where you can do it, where I've seen it done, is in subjects that are going to get a cochlear implant. And just before the electrode – the typical approach to this is inserting the electrode through the round window membrane and then advancing it a significant way towards the apical portion of the cochlea.

Well, we were aware of a group in **Hannover, Germany**, who is probably one of the world's busiest cochlear implant centres. And what makes this group unique is that every patient that comes in for an implant, just before they put the electrode in, they collect a sample of perilymph, and it's a very specific technique, a very careful unique that they have to do. But they are able to collect a small volume of that fluid. And their research project is, it's a proteomic analysis project is, it's a **proteomic analysis** programme, they're looking at what proteins are expressed within the perilymph, and how does one associate that with whatever the inner ear disorder might be of that particular cochlear implant subject.

So we approached the Hannover group and we asked them, "Do you think that you could administer FX-322 in the operating room and then, just before you're going to insert the

electrode or just when you're going to collect a perilymph sample, we would like to take that sample and analyse it for drug levels." So that is the combination of two groups: our therapeutic and their expertise in cochlear implantation and collecting cochlea fluid samples. So we embarked on a study, we started it last year, and recently we shared the results publicly, so we dosed 7 subjects, every subject got FX-322, and about 60 to 75 minutes roughly later, into the surgery, that's the point where they're about to insert the electrode, they collect the perilymph. And so, we were able to analyse that perilymph sample for our two drugs that make up FX-322. And what we're able to conclude from the results of this study is that both of our drugs are detectable in the cochlea.

And then there's a big question, as where do they go in the cochlea. We're measuring them just in one spot. So, what one has to do, is we use a computer simulation model that we developed with a collaborator based on some preclinical work. And if you take the levels that we derived from the human cochlear implants and you impute them into this computer model, the model can predict what the distribution and the time course of concentration will look like in the cochlea. And so, when we did that, the model predicts for us that we are able to achieve pharmacologically active levels in the human cochlea.

So those are the two pieces, and then the third piece is, we haven't talk about this, our Phase I data yet, but the Phase I is really the signal, it's the hearing restoration signal that we've identified. So we now believe that we can get our drug there through a very simple office-based procedure, intertympanic injection, the drug levels that are in the cochlea are predicted to be pharmacologically active and, based on our Phase I study that we did in 2018, we see this remarkable improvement in particular in speech intelligibility in many subjects. If you can check those three boxes, it really indicates that we're going in the right direction and we're really happy about those recent results and as I said couldn't be more enthusiastic about moving forward on our programme.

**Jackson:** Yeah, it's very interesting and I've never heard any of that background to – I suppose that was preclinical when you measured the perilymph concentration of the drug?

**Carl:** We've done a lot of work in multiple species to characterise how the drug behaves within the cochlea, and then you can almost do by allometric scaling, you can almost predict then where the human will be, because the human cochlea is typically larger than most of the species that we work in.

## 24:48 Results of Phase I clinical trials

**Jackson:** Right. And you mentioned something about your Phase I clinical trials and I'd like to just start by touching on some of the improvements in hearing that you've measured, because usually Phase I is for safety, but you've managed to secure some efficacy data as well, it seems.

**Carl:** Yeah, we called that a safety study, because the two drugs that make up FX-322, one of them is a very well-known generic drug called **sodium valproate**, it's valproic acid, it's sometimes called Dapacone or Dapacode, it depends on the brand versus the unbranded name, and that's a drug that has been used to treat status epilepticus, sometimes it's been used for migraines, so there's a lot of safety data available with systemic dosing, with IV and



oral dosing with that drug. Now we're only taking a tiny amount and put it into the ear, but we liked the concept of having a generic well-characterised drug as one of our molecules.

The other molecule is a proprietary molecule, and this is a molecule that goes after a specific pathway, and as I said earlier, it's the combination of these two agents that we think is important. But since we were taking a new molecule that had never been tested in humans before, we were taking it into the clinic for the first time, we wanted to conduct a very careful, rigorous, randomised, double-blind, placebo-controlled study. And as you say, most people don't do that for Phase I. But we thought it was important, just to give us confidence on the safety side.

So we designed this study, and we conducted it in **San Antonio, Texas**. And we chose that location because we were able to identify three private ENT practises in the San Antonio area that were interested in participating with us and felt that they could recruit subjects from their patient populations. And that was important because one of the designs of the study was, we had a requirement to be characterised as being stable, and we determined that stable meant there couldn't be any significant changes to your audiogram for at least 6 months. So usually, individuals that are part of these practises that typically come in once a year, sometimes twice a year to get their hearing tested, that population is very motivated for hearing health and want to be monitored carefully. So we recruited from that group, and again, they had to have a historical audiogram, there could be no changes for a minimum of 6 months.

So then, the next component of the design was this double-blind, placebo-controlled trial. So we were interested in recruiting two different groups of hearing loss individuals, firstly those that had histories, medical histories that were consistent with lots of exposure to noise. So in general, it was usually occupational noise exposure. The San Antonio area has a heavy ex-military population, and so a number of those individuals got exposed to noise through those means. And then the other group of individuals that were part of the study were what are called **idiopathic sudden sensory hearing loss**, so that's a loss of hearing, no-one knows why, sometimes people believe it may be viral or it could be vascular, but no-one really truly understands the reason, but what we know is that it's associated with a loss of hair cells, if it's permanent. Now, the acute phase, but if it's permanent, it doesn't return. So that group of permanent sensorineural hearing loss patients is what we took into the study.

And again, no-one knew who was getting what. The subjects didn't know what they're being dosed with, the physicians doing the injections didn't know what they were giving, the audiologist doing the test didn't know what the subjects had received. And importantly, we didn't know, we can't know, that's a critical design feature of doing double-blind, placebo-controlled trial. We can't have no influence whatsoever on the study, we have to be completely independent from the activities at our trial sites.

One last feature that we included in the study design is we dosed only one ear, so some subjects that come ear have hearing loss in both ears, but we typically would dose the worst hearing ear as long as it would qualify according to the requirements. And we were looking at mild to moderately severe subjects, that would be based on their pure-tone averages. The reason we chose that group, if you mention, had we gone into a more severe patient setting, and if our drugs would have a safety issues, it would be difficult to see a potential worsening



of hearing. So we selected a group that had still existing hearing function, and again this mild to moderately severe category is what we decided.

So, just to reemphasise these points of control, because I'm going to come back when we talk about the results: stable patients for at least 6 months, placebo-controlled, double-blind, and we only dose one ear, but we monitor both ears. So, individuals were given a single injection, we monitored them carefully for safety, and then two weeks later they came back for their first hearing test, and then every month thereafter. So they received one injection and then they were essentially monitored for three total months. And we were blinded, we were monitoring the data, just to make sure there were no issues with safety.

And we did notice that there were several individuals that were showing improvements in one of their measures of speech intelligibility, and in particular this was the Word Recognition Test. So the way that we do that test is through headphones, and we were always testing one ear at a time, and in this study, we used a 50 word list of all monosyllabic English words. And it's a recorded voice that's played at a certain loudness, and we set that loudness. And the voice will say: "Say the word chore." C - h - o - r - e. And we're listening if the subject gets it correct. And if they get it correct, we record that. And if they get it wrong, we actually record the wrong word. So this example of "chore", you could imagine an individual might hear it as "shore", s - h - o - r - e, that is really important information in the word they may have gotten wrong. And we analyse down to that level.

So that measure appears to be very sensitive and, as I said, as we were monitoring the data, we noticed there were several individuals that were showing improvements in one ear and we knew it was the treated ear, we just didn't know what they had received, because we were all blinded to treatment. Well when we completed the study and analysed the data, and we broke the blind, lo and behold, the only improvements that we observed looking at the Word Recognition Measure or speech intelligibility was in the ears treated with FX-322. And in fact there were 4 patients, 4 ears treated, that had at least a doubling in their word scores, which none of us had ever seen before. We've shown this data to the world's experts in this field, and no-one has seen ears do this before.

And so the question was: O.k., well, how can we convince ourselves that this may be a hearing signal? Well, I come back and emphasise. We know that we were looking at stable patients, so there was no fluctuation as they were coming into the study. We only saw the improvement in ears that were treated with FX-322, those improvements were not just statistically significant, but clinically meaningful improvements. And another component is, since we were double-blinded, no placebo ear had any improvements. And then the last component is, no untreated ear had this kind of improvements.

So there were many controls built into the design, and we believe that what this data indicates to us is two things: firstly, it's the first evidence that using FX-322, the first evidence with a potential hearing restoration therapeutic that you can improve the clarity of sound or improve the intelligibility to a subject, which means the most to them.

And secondly, the fact that there's no placebo effect, I kind of go back to my drug development heritage here, when you do trials, you're always wondering what your placebo phenomenon is going to look like. When individuals participate in placebo-controlled trials, everyone hopes

they got the drug. And that hope changes you, it changes your focus, it can change your general wellbeing. You may subjectively decide to change things in your lives, because you are hopeful that you got the drug. And some of those changes can have a bearing on measures that we build into clinical trials. What is unique about this is, if you give somebody a placebo in-ear, they cannot think they got a drug and suddenly hear better. The metaphor would be, you know when you go for a vision test and you squinch your eyes, you can see a little better. Because squinching changes the shape of your eyes, but you can't squinch your ears. You can't squinch your ears and suddenly hear better. That's just no phenomenon that we are able to do. So we think that the results from this, again small, Phase I safety trial are truly remarkable and give us great confidence that we have for the first time shown a signal, a hearing signal in individuals, that basically had permanent hearing loss in that ear.

**Jacksons:** Yeah, it is very impressive. And we're glad you went to the length that you did to validate the drug. Obviously the placebo effect is a very well-known psychological phenomenon, but less applicable in very fine – like you said you can't squint your ears, you can't strain harder to hear something. So, it's nice to have that validity.

### 36:00 Potential effects on tinnitus and speech intelligibility

**Jackson:** We're going to move on. So, we've seen that you have amended your outcome measures somewhat for your Phase II trial to include an evaluation of tinnitus using the Tinnitus Functional Index. Further you have expanded your audiometric testing to evaluate FX-322 and its effect on ultra-high frequency hearing. Are these new outcome measures in response to something that you have found in your Phase I clinical trials?

**Carl:** As I mentioned before when we were talking about the relationship between, if one could restore outer hair cells that function as filters and tuners, if you could restore those, then one could create a hypothesis that you might also provide a benefit to tinnitus. We don't have any data, but there could be a biological rationale in it, and for that reason we have decided to include the TFI, which is the FDA's preferred instrument for determining the effect of tinnitus on daily activities, so that's the first component.

Secondly, the expanded high-frequency range was really based on data. Part of it was pre-clinical data, when we were analysing the distribution through a number of different species. And the data that I have described from our collaboration with our team in Hannover Germany and the cochlear implant subjects, those two projects, when combined, essentially lead us to have the understanding that our drug, when they are injected inter-tympanically, primarily concentrate in the highest frequency range. Now I can't say exactly what that frequency range is, but it would be in the higher range. And for that reason, we included measuring up from 9.000 to 16.000 Hz.

Now that's important, we believe that's important. If one kind of looks up the history of traditional acquired sensorineural hearing loss, you start losing your hearing from the highest frequencies first, because that is where sound comes in, it's those highest frequencies first and then eventually makes its way to the lower range. So in this case, we think that our drug is concentrated in the right place, we do, however, have a big effort in drug delivery, we are aware of technologies that one can use to kind of modulate the distribution of drugs through the cochlea, and that's something we're looking at very carefully. But we think for a first

attempt here, at a hearing restoration therapeutic, we really liked the properties that FX-322 is showing us.

**Jackson:** Yeah, we were very interested because a lot of people who experience tinnitus have that very high pitch, kind of ring which, we assume, would be associated with ultra-high frequency hearing loss, or the very least high-frequency hearing loss. So we had sort of suspected that – since its concentration is best towards that base of the cochlea which corresponds to the higher frequencies, we had suspected that it might have a profound effect on tinnitus. But were there any anecdotes or patient testimonials that kind of corroborate our theory?

**Carl:** Again, we don't have data. Certainly there is anecdotal reports as patients have come back and visited with ENTs when they have had conversations with them about how they are doing. Some of them have offered that they have had improvements in tinnitus, there's nothing that we can quantitate there. Again, it adds to the excitement of the opportunity.

And in your comments about the extent of high-frequency range, we haven't spoken too much about one of the other measures that we used in this one study, the **Words in Noise Test**. This really gets to the real-world setting that many of us struggle with. I have high-frequency hearing loss in one of my ears, and I have to adjust and accommodate for it when I'm – certainly not at restaurant these days, but if one is in a public space and there is noise in the background, it's really hard, it's harder to hear, it's the hardest test for our subjects in our trials. And there's a lot of important information in that high-frequency range. So, you know, the way we test for this is the Words in Noise Test, or the WIN Test.

When subjects have the headphones on, what happens is, we bring in through the headphones background noise in the form of multi-talker babble. In our case we use – it's six voices all talking at the same time. But you can't distinguish what one of the voices is saying, you just hear six individuals talking. And then we bring the words in. And again, say the word "chore", but with multi-talker babble in the background. So it really tries to replicate the real-world setting, and we think that can be an incredibly exciting measure for us. We did see a hint of the signal in our first trial, it wasn't statistically significant, but we were encouraged by the pattern that we observed, that there were similarities between the quiet background test, the Word Recognition Test, and the Words in Noise Test.

All this lines up for a therapeutic that is providing what we think to be the most important thing, which is intelligibility. Our Chief Medical Officer here, he has said to me, you know, when you think about an individual coming into their doctor's office, the first thing – they don't state as a complaint "Oh doctor, I lost 10 dB in my 8.000 Hz range." They don't know that. But what they complain about is, "I have to turn the television up louder. I can't hear my family member from the other room." Those are the things that matter. And that's why we think the intelligibility measures are so crucial to understanding how the drug works.

**Jackson:** That's interesting. I have a question later on about that, but I guess we can just address it now. So you think the increases in speech intelligibility in noisy backgrounds, they're not clinically significant you said, but still improved upon. You think that's more a product of restoring the high frequencies/ultra-high frequencies rather than a potential **cochlear synaptopathy** that this drugs also may address only in areas where the hair cells are actually

destroyed. But – at least on the forums it's understood that the Words in Noise Test is sometimes a test of cochlear synaptopathy, where the nerve itself is having issues, sort of interpreting the signal, but rather it seems that you think it's more a product of loss in the high frequency or ultra-high frequencies.

**Carl:** Well, it could be a mix actually. And so, if it's a loss of hair cells in the extended high frequency range, that would be something more direct to how we believe FX-322 works. But remember when we were talking earlier about what happens during the third trimester, it is these progenitor cells, these are pre-programmed stem cells and they're active and they're on and they're replicating and forming hair cells, when that happens, there's a lot of genes that are turned on, because when these new cells form, they have to be connected, right? So, you have these axonal projections and these afferent nerve fibres that have to kind of lead to the spinal ganglions. All those connections have to be made, and making those connections are under the form of a number of genes. And we know those genes are active in development. When we've been in our third trimester, we know they're active. So, if we're able to activate them with FX-322, then one could see it's possible, but you might be able to provide support to synaptic connections and neuronal survival and neuronal support. So it's possible, it could be a combination of those. It wouldn't be the first drug if it gets approved, where one didn't fully understand the mechanism of action. You know there are a lot of interesting opportunities as we continue to study the biology.

#### 44:56 Stimulating progenitor cells – does it work for all?

**Jackson:** So you mention the mechanism of action, which we suppose currently that it's predicated on the support cell population in the inner ear, you mentioned the LGR5 positive support cells. Is there any concern as to the native population of support cells being a determining factor as to whether FX-322 will be able to be efficacious especially in people with more devastation in that area, in cases of more severe trauma?

**Carl:** Yeah, that's a really good question. Obviously we believe the target for the drugs is the progenitor cell or support cell, so it has to be there. And as you say, there could be certain conditions where those are damaged. Or they are no longer intact. There's no question that one could imagine that in older individuals that may have cardiovascular abnormalities or other comorbidities, one could imagine having that result in sort of a flattening of the epithelium within the inner ear. And that could be difficult, to access those progenitors.

I think that when one takes a step back, though, and looks at sensorineural hearing loss as a whole, you know, we think that it represents a good 90 % of the population of individuals with sensorineural hearing loss. And we've done a lot of work looking at temporal bone sections of individuals that donated their temporal bones to science. And we have a lot of information on what their audiograms look like and what their inner ear looks like, and in the vast majority of those sections one can observe the presence of the progenitor cells. So, we think yes, there may be a small percentage of individuals, their progenitor cells are no longer functional or intact, they may not be candidates for FX-322, but we think, the vast majority would.

**Jackson:** That's very exciting to hear, and I'm sure all our listeners very much appreciate that kind of optimism, because there is a lot of worry concerning something that it's so not well understood that – they worry they might be in that minority and they don't know how large a

proportion that minority is, so I'm glad you touched on that. Could you talk about the range of frequencies briefly that FX-322 is looking to cover, is there any aims in the future regarding its level of penetration or the frequencies it aims to restore, possibly lower than the higher frequency that it's currently being measured at?

**Carl:** Well, as we talked about the current trial, it is measuring from 250 Hz all the way to 16,000 Hz. And the other design component of a Phase IIa study that's running is comparing different numbers of injections. So, we have one group that gets a single injection of FX-322. And then there are two other cohorts of subjects, one group gets two injections, and then there's a third group that actually gets 4 injections of FX-322. And each of these injections are spaced one week apart. So, when we think about, you know, how might that translate in the cochlea? If you can imagine, you do an intertympanic injection and the drugs diffuse into the cochlea, and there's a wave of the drugs kind of rolling through a certain range of the cochlea. And then they get eliminated and we – based on our work we know that's going to be mostly in the highest frequency range. Then, a week later, they come back and get another injection of FX-322. And it's possible that that now second wave of drug may not look identical to the first wave. Maybe it hits 10 % more progenitors or maybe it gets to a lower frequency. And then you come in with yet a third and yet a fourth injection, so we don't understand this yet, because that's really difficult to model pre-clinically, but the current study is designed to address this question, do you get greater benefit with more injections of FX-322 compared to a placebo group?

### 49:28 Asymmetric division – what differentiates FX-322 from other hearing regeneration approaches

**Jackson:** Ah, that's very – I'm sorry – That's very interesting that you mentioned that, it's actually one of my follow-ups, is regarding the issue of continuously better returns upon administration. Do you suppose that that has to do – I don't know – there's some information regarding its effect on support cells. And it was in the **JP Morgan Q&A** that was published on March 20, as a corporate overview in March 2020, that mentioned the asymmetric division of the native support cells, DR5 positive support cells, but what interested me was the term "the asymmetric division". Does this sort of indicate that it could split into an active progenitor cell in addition to possibly multiplying the support cell itself, and could that be the mechanism behind potentially continuous returns on the drug?

**Carl:** Great question. So the way – I recall a presentation by my colleague **Dr Loose** – the way that we think about this is that when the signal comes in, in this case the signal that we're giving is FX-322, you have now given a quiescent or dormant progenitor cell, they provide support and they communicate and they provide nourishment and such, but that's not what they do in development obviously. So, as the signal comes in, you – we believe what we're doing is we're coaxing them back one step in their development cycle, so we take them back to a bi-potent stage of development. And that signal to go back is – you suddenly now activate the pathways that you need, and all the genes are now starting to turn out that you want, and that first signal we believe to be this asymmetric division.

So you're forming now a new daughter, a progenitor cell, which is crucial. And then, importantly, a new sensory hair cell. And that sensory hair cell could be an outer, could be an inner hair cell. Whatever is missing, that's how we believe it's sort of programmed, because it

tends to be a 1:1 relationship, every hair cell has their sort of partner progenitor cell. This mechanism that, we believe, takes place is unique and different from what others have tried when they're using single small molecules, or sometimes they're using gene therapy. What those programmes have tried to do is take a progenitor cell and – it's a process we call trans-differentiation – you're taking a supporting cell, a progenitor cell, and turning it into a hair cell, you're making it want to become a hair cell. The problem is, it can't be a fully functional hair cell, because you haven't turned the right genes on. And the other problem is, you have now exhausted now your progenitor pool. That progenitor won't be replicated, it won't be replaced via the asymmetric division process that, we believe, one needs. And we believe that's important because that's the way that nature intended it to happen, it's exactly what happens during development.

So we think it's a good approach to take, we think so far since we've had a very favourable safety profile in our clinical trials and our pre-clinical programme to support that. It's the right way to do it, and it's a well-tolerated way to do it, but different, others have different approaches, and we want others to succeed in this field. This just isn't going to be one approach. But we have strong belief in the course that we're taking.

### 53:25 Potential overgrowth concerns

**Jackson:** And we do too, especially me, I've been a fan of FX-322 for a while now, and we realised the difference between basically creating the birth of a whole new cell that isn't retro-fitted through sort of different approaches, from **Audion**, which may deplete the native cell population, which – so you suppose that FX-322 doesn't appear to do so, it doesn't appear to deplete nor could it actually replicate more support cells?

**Carl:** No, there's no – we've done a lot of other pre-clinical studies, the basic toxicology studies that we have to do to support human clinical trials. In none of those studies did we see any indication that there might be an overgrowth or stimulating too much asymmetric division, so we've not seen any of that. And as I said, no indication in our clinical trials to date that there would be any concern with the safety signal. So, again directionally, this looks very favourable to us.

### 54:37 Potential benefits for 'hidden hearing loss'

**Jackson:** O.k. Great to hear. When **Dr Loose** was asked about cochlear synaptopathy during **Frequency's JP Morgan Q&A** he responded that it could treat cochlear synaptopathy in cases where regeneration occurred in the hair cell, and its subsequently newly formed synapses. For clarification, is this in reference to the inner hair cell synapse with the spiral ganglion neurons, and is this subset of regeneration what is proposed to be behind those speech and noise improvements? I suppose we touched on that earlier. So we can just be brief about that.

**Carl:** Yeah, I think that just that explanation you gave, Jackson, would be a reasonable hypothesis to what might be happening, you know. In the case of cochlear synaptopathy, you know, we've heard it described as hidden hearing loss, but it's only hidden because people haven't been looking in the frequency range that we think one needs to look. And so I think there's a greater appreciation that we as sort of living in this industrialised society, we are losing function in a region where no-one really has spent much time looking. And I think the



reason for that is primarily because hearing aids in general can help one up to about 5.000, maybe 6.000 Hz. And anything higher than that, one tends to get a lot of distortion.

And the other thing, too, is that hearing aids don't really help in a noisy background. So if one can imagine that you're restoring hair cells in the range, in this extended high-frequency range, and some of those might be outer hair cells that are doing the filtering and the tuning, and then some might also be inner hair cells, that are then giving now the sort of neuronal reconnection synapses and spiral ganglion. Then it's almost like a double-header. So, you know, we think that these measures are important and give different insights as to what might be happening biologically, but all pointing in the right direction which is restoring intelligibility, which we think is just so crucial.

**Jackson:** Yeah, is there any – has there been any pivot from like pure hearing restoration to the clarity and intelligibility, is there any reason that there would be sort of a shift in goals towards covering what hearing aids aren't?

**Carl:** Well, I think that we would expect that the data that we derived from these trials was kind of driving in that direction. Our first experience on this first trial would indicate that. The most sensitive signal was intelligibility. We might have seen a few individuals that had 10 dB improvements at 8.000 Hz. A small number, again these would only be ears that were treated with FX-322. But that's the reason that we really want to look higher. It's possible, but one could imagine seeing a signal, seeing better audibility in that extended high-frequency range, and if that's the case – it's, like we talked about it – there's important information that has been neglected up there. And when we talk about language, and we talk about consonants like fricative consonants, these emit very high energy in the extent of the high-frequency range, and if you have lost that function, you can't hear the definition and the clarity of those words, and now you have got a challenging communication. So it seems like that can be an incredibly powerful mechanism, if that's the case, that we think will translate to a very clear benefit, the data coming out of the study is going to tell us that.

**Jackson:** Yeah, we agree. We think that a lot of the important information in this ultra-high frequency is kind of being lost over in terms of typical measures of hearing, with most ENTs only testing up to 8 kHz, and it's very difficult to even get a grip on where your losses are, and if they are integral to your hearing, so we're glad you're investigating those avenues, giving them their due diligence. However, there has been some confusion regarding the drug's efficacy on damaged but not destroyed hair cells. I don't know if this would be something you would be able to speak to at this point, but could the drug affect damaged but still intact hair cells, in the event that they weren't ultimately destroyed during whatever the traumatic event was?

**Carl:** I think we don't know the answer to that. Our pre-clinical work, the pharmacology model that we have used to really kind of put FX-322 to the test before bringing it into humans was a noise-induced model, pretty severe trauma. And we did this work in mice. The damage in that model goes above and beyond the traditional acquired sensorineural hearing loss. So if that's evidence in such a severe model but we could restore function, but we could restore hair cells, I think it opens the opportunity to do both of the things that you were just describing.

## 1:00:06 Potential benefits for restoring damage from ototoxic medication

**Jackson:** That's good to hear. Are there any thoughts on whether or not FX-322 could be efficacious in populations with ototoxicity? We know from, let's say medications, we know that you're testing on noise-induced right now, is this a strategic decision to kind of narrow your focus on something that's more well understood, or is there something about ototoxicity that scares you off from including them in your patient population?

**Carl:** I think it's – we want to study any aetiology that would be represented by acquired sensorineural hearing loss, so right now while we're doing noise-induced and idiopathic sudden sensorineural, I think we have a genuine interest in looking at age-related. There's a population that we just refer to as pre-presbycusis, so it's younger than 65 but there's no evidence of noise exposure, and then the ototoxicity group, definitely. The two most common settings would be with cancer chemotherapy, in particular cis-platinum or platinum-based, and the other one would be amino-glycosides that are associated with quite a bit of hearing loss, to such high doses given systemically, in particular in cystic fibrosis folks. So, I think we are interested in eventually looking at all of those areas.

**Jackson:** Great to hear, I'm sure all of our ototoxic-induced folks are definitely paying attention and hanging on every word, we thank you for touching on that.

## 1:01:52 Getting the drug to market – FDA fast track

**Jackson:** I'd also like to thank you for how, like the brevity that you guys are acting with. You guys seem to have a sense of urgency about getting this to market, and we were very excited when FX-322 was granted fast-track status by the **FDA [Food & Drug Administration]** in addition to **Mr Lucchino's** mention on **Bloomberg Radio** that FX-322 could be branded a break-through therapy by the FDA. This is something that we were tossing around for a few months and hearing him breathe it into fruition was refreshing. How do such designations, such as break-through therapy and fast-track status affect the release timeline, and is there any possibility that FX-322 could be granted conditional approval, which would allow you to skip Phase III in clinical trials?

**Carl:** So, the designation of getting fast-track status really allows us to have more interactions with FDA, which is important especially at an early phase. And we've talked publically about, on the basis of the Phase IIa results, if those results were positive, we have every intention to file a request for break-through designation. So what that in general allows one to do is again continue to have more and more interaction with this division of FDA, and there can be a situation where, again depending on what the data looks like, depending on the safety, one can kind of speed the process along even faster. At this time we can't make any comments about whether there would be a concession for not having to go through a certain phase. Right now, our plans are, you know, we're in kind of in the middle phase of development, which is Phase II. We are assuming we're going to have to go through a pivotal phase, which would be Phase III. And that would be the next phase we want to go to, and as I said, we're working as hard and as fast as we possibly can.

**Jackson:** We definitely see that and we certainly appreciate it as a community to see that sense of urgency from you, because there has been a lot of excitement before in the community. I wasn't present for it because my onset was last year, last summer. But it seems that we've kind of been led along sometimes, and in many cases the day never comes where we see something hit, hit us that is actually very optimistic and efficacious for our very specific suffering, so we're glad to see somebody in the driver seat.

**Carl:** What I've said publically in other settings is, this is a partnership. We can't do this by ourselves. So it's going to require partnership, clearly with the health authorities, the FDA, but it requires a strong partnership with our investigators, our study participants, the site staff, the patient advocacy groups, the professional organisations, I mean we're going to have to mobilise everything here to keep moving this forward. And so that's our intent, we want to partner with all of these key groups, because we can't do it by ourselves.

**Jackson:** Right, and we see that you're making presentations all the time and trying to reach as many people as possible for these crucial partnerships, so again we really thank you for that.

### 1:05:13 Expanded access – compassionate use

**Jackson:** Dr LeBel, on your website, you explain that you currently prohibit the use of expanded or compassionate use due to currently insufficient clinical data and lack of production resources. Is that policy something that could be reconsidered in an event where Phase II trials reveal significant efficacy for the target populations?

**Carl:** Yeah, I think our approach will be, anytime there's a significant set of new data that comes in that helps us understand, firstly and importantly our position on expanded access is due to really the fact that we don't fully feel that we've been able to characterise the safety profile of the drug yet. And so loosening the philosophy of sharing drug, this is a hard time to do that. We don't understand the risk-benefit profile just yet. So I think that we're certainly interested once we get this next set of data that we can revisit that based on what the profile looks like. But at this time we have to stay with that policy.

**Jackson:** So you think this is something that will possibly reveal itself in your current phase of development?

**Carl:** We think so, yes.

**Jackson:** That's excellent to hear, because there are many in the community that would, I mean, they would die to get – to become a part of this trial, they'd die to get their hands on this drug, me being one of them. But a lot of us are excluded due to trial parameters which are stringent for very good reason. So we just really want everything to go as swimmingly as possible, if we can't participate in them ourselves. So, yeah, we're glad to hear optimism on all fronts, so I'd really like to thank you for joining us, it's been a pleasure to sit down with you. And thank you for making time. Thank you Hazel for having me on the podcast.

**Hazel:** Yeah, you were a great addition, Jackson. I mean, I was leaning back 90% of the time and letting you guys chat, so it was a very easy job as podcast host.

**Carl:** Well we, on behalf of Frequency, we appreciate the conversation that we got to have with you. Hopefully the listeners will enjoy it as well. And, as I said, once we get our next set of data, we're optimistic and we're hopeful that that will continue to be positive and we'd love to come back and talk with you again.

**Hazel:** Oh, that would be great. We would be delighted to have you back, Carl, and once again on behalf of the Tinnitus Talk community, thank you so much for sharing your time with us and sharing so much valuable information and insights with us today.

**Carl:** It's our pleasure.

### 1:08:00 Bridge: introducing our debrief & disclaimer

**Hazel:** Hey there, we hope you're still listening. Now, if you're interested, we have our debrief coming up, where we'll discuss our impressions of the interview and explain some of the more technical concepts.

Before that, I just want to say that we don't have any commercial ties with Frequency Therapeutics, or any other company for that matter. This episode is not meant to be promotional, but informative. Of course, we cannot yet know if the company's drug will work, because the hard data isn't there yet. But just the fact that there are companies like Frequency working on solutions is in itself heartening and we all could use some hope.

Alright, anyway, I'll stop here and let you listen to the debrief.

### 1:08:53 Debriefing: Jackson's impressions

**Hazel:** Jackson, what are your first impressions about the interview we had just now with Carl?

**Jackson:** I thought it was very optimistic, I think he met all of our questions with a lot of detail. I think he was very positive in terms of the direction that they're going.

I think there was maybe a little bit of confusion, I don't know if it was with the wordage of the question concerning the native cell population numbers. I think that he kind of regarded it as almost a safety issue if the support cells were to multiply, whereas I was kind of trying to gear it towards an efficacy question in terms of, if somebody has a more devastated native support cell population, is there any potential for some kind of replication of those with the induction of FX-322. And I think he answered it more in terms of – it has a favourable safety profile, it doesn't – maybe it doesn't like almost proliferate dangerously, almost like cancer. This is kind of the way I interpreted it.

So, yeah, that was really the only thing that I would have liked to have gotten a little bit more in detail, but we had to press on because we had more important questions to get to and we weren't able to address two important ones. So that's very regrettable, but other than that, I think it went very well and it was pretty straight-forward and didn't get too into, it didn't hammer us on the head with the science. I think he put it in very conceivable terms.

**Hazel:** Yeah. I think, well for a completely lay person it's probably a little bit heavy on the science still, even though he explained things very clearly. But we'll try to clarify a bit more in our debrief for the listeners. But yeah, we did have limited time, of course. That happens when you interview busy corporate executives. So, what were actually the burning questions that you didn't get to ask?

**Jackson:** This one goes out to our hyperacusis community. We didn't get to address as to whether or not FX-322 could address pain and/or loudness hyperacusis. The reason that I kind of put this on the back burner... that wasn't a conscious decision. I didn't have like some questions just in my pocket where I was like, "O.K, those are the ones that are going to go", but as I scanned the interview paper, I don't think they really had any way of answering this like appropriately that would give us any sort of satisfaction, because it's not in their secondary outcome measures. It's unfortunate that hyperacusis is so poorly understood, but I don't think that there's anything that they could have spoken to, although Dr LeBel mentioned that he would be willing to speak with us again, so we'll hopefully have an opportunity to address this especially upon release of Phase II trials. So, just hang tight, I know the hyperacusis situation is sometimes worse than the tinnitus population; that's originally the way that mine was, I was – I had an absolutely horrible hyperacusis after the airbag blew up in my ear, that's also what led to the tinnitus, but – so I know how bad hyperacusis can be. So, I feel for you, guys, I wish I could have gotten to this, but I promise we will get to it next time.

**Hazel:** Alright. And what was the other question?

**Jackson:** There were actually two more. There was the plan for international clinical trials in drug release, we didn't know if they were going to combine them for Phase III, so that they can release in Europe and USA. And then there was: "Has the outbreak of COVID-19 significantly affected the conduction of trials and release timelines?" And I think that they – not only do they touch on that with their chats, they do a lot with keeping people up-to-date on what their plans are, where they are.

**Hazel:** Yeah, I was going to say, because, well regarding the COVID thing, I listened to a couple of their recent, you know, webinars or broadcasts and I think they did communicate about that extensively, so, but maybe you can summarise it for our listeners?

**Jackson:** So, COVID hasn't really affected Frequency's approach as much as it possibly is affecting other methods, other companies, because their trials are conducted in actual ENT clinics. Their patient population is more ready, more available. They've had a little bit of a hick-up in terms of new patients being admitted to the trials, but it's not like all of their progress has been halted. So, I decided to put that on the back burner, because we can just touch on that here.

**Hazel:** Was there anything really that you learned that you didn't yet know about?

**Jackson:** I think I knew the stuff about the stomach lining, I knew the stuff about the origin. I'm glad he touched on the tinnitus patient testimonials, because that was a hard one for me. It was not an outcome that they were measuring, so it could have been one that he would

have dodged and said “well, we didn’t measure anything”, but he openly answered that there was some anecdotes that hadn’t been monitored, so it was nice that he could give us a lift.

**Hazel:** Yeah, right. There’s no real hard data, they didn’t measure anything, but they did hear informally that tinnitus might have been affected for some. And we, again, don’t know any more details than that.

Well, I’m very happy that you were doing the interview with me, Jackson, and we were able to cover these more technical issues that I didn’t feel well positioned to. It was nice for a change not to be the only interviewer, and I have to say you’re a natural, you did splendidly.

**Jackson:** Well, I really appreciate that. I think everything was set up for my success, so I really appreciate the lengths that you guys went to, to ensure that we had proper audio quality, that **SquadCast** was working. So again, thank you both for that. It was really a privilege to be on here, and I really appreciate you guys taking all the time to sort out the technical side, especially being international, dealing with, you know an American in Ohio, in the **Akron Recording** studio, I’m glad that everything went smoothly. I’m glad that we got out the questions that we needed to, that it wasn’t too much stress on my side at all, I just had to show up and everything was set up for a success. So, I appreciate that, and I’m glad to be on the frontlines of, you know, very important, very positive information, because we all need it in a time like this.

**Hazel:** Absolutely, yeah. And you got a little taste of podcasting in the process as well.

**Jackson:** That’s right, so. I’m ready for round two, whenever.

**Hazel:** Yes, they did agree to that, so I’m looking forward to it.

**Jackson:** Yeah, absolutely. Alright, thank you for having me on, again, and yeah, I’ll be waiting in the wings. I’m sorry I’m not as much of a presence online anymore. I’ve been dealing with side-effects from medication that is less than ideal, because of the tinnitus that I have to take the medication, so I’ve been doing everything I can just to get through the day, and right now it’s kind of at that point where we’ve reached kind of that information apex where I think I pretty much know ultimately what I need to know, especially after this interview, where I don’t even know if I’d be able to add anything to the discourse. And it’s tough seeing a newcomer come in and struggle, and knowing that I’ve been there and yeah, it’s tough to get back on there, but I still I check in every now and then so, yeah.

**Hazel:** Yes. I’m sorry to hear that you’ve been struggling, and of course, everyone understands if you have to focus your energies elsewhere, but we do also always really appreciate people like you, more experienced people sticking around to like advise and inform and support others, so we appreciate you being around.

**Jackson:** Yeah, absolutely. If anybody has any questions or anything, my name’s **mrbrightside614** on the forum. Oh yeah, and I want to thank **FGG** for being on the call with me to add crucial bits of intel such as ‘we’re running out of time’, and making my heart race a little bit more, but she was, she’s great, we’ve built such a relationship because of this project



that we're on, creating the questions, and she braved the trip even through her visual snow and everything that she has to – so I'm really happy to have her here.

**Hazel:** That's really great that she made the, what is it, 8-hour trip and it's always great to hear about Tinnitus Talk members meeting up in person and striking up relationships, friendships, etc. Yeah, that's really awesome.

**Jackson:** Yeah, we're all we got. It feels like...

**Hazel:** Yeah, that's one of the – well, I mean, honestly, I mean that's one of the reasons, that's why Markku started this whole thing and why we put so much time and energy into it. I mean there's many reasons, of course, but that personal support element, that's how it all started, right?

**Jackson:** Yeah, people just don't realise it unless they have it as a moderate to severe version themselves that it can devastate people, so...

**Hazel:** Derail your life, yeah.

**Jackson:** Yeah, so, glad to be here. Glad to have you guys, glad to have the community. And shout out if you need to, I'll try to get around to it, to keep you abreast of how my situation develops, and hopefully, yeah, eventually get onto the healing road, I don't know.

**Hazel:** Yeah, fingers crossed. Alright, thanks Jackson.

## 1:19:46 Debrief: FGG explains technical aspects of hearing restoration

**Hazel:** Debriefing a little bit further on the Frequency Therapeutics interview, I'm joined here by another one of our Tinnitus Talk members, her username on the forum is **FGG**. She's very knowledgeable on hearing in general, and specifically hearing regeneration techniques. We thought it might be useful to chat with her a bit and get a bit more background on, you know, some of the technical parts that were discussed during the interview with Carl. During the interview, we didn't really have time to explain all the technical terms to people who are not familiar with them, so hopefully FGG can provide us with a bit more insight. Welcome.

**FGG:** Thank you. I'll do my best to explain.

**Hazel:** Yes. So where should we start? Can you try to explain in lay terms how FX-322 works, because we heard terms like 'progenitor cell', 'support cells', what are those, like, can you try to put it as simply as possible?

**FGG:** Sure. I think Dr LeBel did an amazing job kind of going over that. But trying to simplify even further, progenitor cells are sort of like a stem cell that's further along the path towards becoming the final cell. And what the drug does, it stimulates a population of these progenitor cells in the cochlea to produce hair cells. This was based on, as he said, a similar population in the intestines that replenished intestinal cells with a very high turn-over rate, so they knew the potential of these cells to regenerate was very high. And they did, by chance, find these

same cells in the cochlea and the drug is designed to stimulate them in a way to produce the target cells in the cochlea, which in this case is hair cells.

**Hazel:** Right, so if these progenitor cells are stimulating new hair cells to grow, what like source materials is it using – is it like turning existing cells into hair cells, or how does that work?

**FGG:** Sort of. And one of the key differences between Frequency's approach and others is that it takes these progenitor cells and it asymmetrically divides them. So, normally, when you have a cell divide, you have two equal parts. And, in this case you have one of those daughter cells, one of those parts, becoming another support cell, so replacing the one that was lost. And then you have the other daughter cell becoming a hair cell.

**Hazel:** Alright. And why is that thought to be a better approach, or what's the theory behind that?

**FGG:** Well, he touched on this, and he said that when you transduce a cell, which means you make a cell into another cell, versus stimulate it to divide, when you transduce a cell you don't make an exact product of what you need – product for a lack of a better word – of what you need. So you're basically taking a support cell and making, and retrofitting it into a hair cell, whereas in this approach, you're going further back and you're making a brand-new hair cell as well as a brand-new support cell.

**Hazel:** Alright. And the theory is that that would work better than trying to turn an existing cell into something it was never really meant to do?

**FGG:** Yes. It's basically starting from scratch and developing into a cell versus turning another cell and kind of retrofitting it as best as possible into a hair cell.

**Hazel:** Alright. Carl also talked a lot about delivery methods and the importance of getting the drug to the cochlea correctly and then to the correct parts of the cochlea. Can you explain a bit more to our less informed listeners why that's so important?

**FGG:** He didn't go into quite the detail that I would need to fully answer that question. But what he did say is that their gel becomes a state in the middle ear that will better diffuse across the round window into the cochlea. And so, this delivery results in a higher concentration than, say, oral methods. That's why it's very important to use the injection, the intertympanic method, where they take a needle and go through the ear drum and they deliver the drug locally.

**Hazel:** Right. So that is a key distinction, delivering it locally versus taking a pill that you don't really know if it really reaches the place where it should be.

**FGG:** Right. So oral methods definitely reach the cochlea in at least some concentration. That's why ototoxicity is a problem, even with oral drugs, but if you need something, you know, a greater amount, local delivery is superior.

**Hazel:** O.K. Could we talk a bit about the different parts of the cochlea and how, you know, it's important that we know which parts are targeted?

**FGG:** What was great is, he actually answered something that's been kind of discussed back and forth on the Frequency thread a lot, which is, does this do outer as well as inner hair cells? And he said it does whatever is needed, which is great, because there's no real diagnostic test for inner hair cell loss that's reliable.

So structurally, the cochlea has three rows of outer hair cells, and one row of inner hair cells. And we have each of these rows across all frequencies. So, from high to low, you have these triple layers of outer hair cells, and below that you have these inner hair cells. And outer hair cells have a little bit of a functional difference. They kind of amplify noise. That's why an audiogram is useful when you're deciding whether you lost outer hair cells. Because it takes a quiet sound, a low vibration, and amplifies it. So, if you can hear, say, 10 dB, then you have good function of your outer hair cells. But if you need – if you have less of them and you need louder sounds to stimulate the outer hair cells because you have less of them, that's why an audiogram tells you a lot about outer hair cell loss. Below that, you have the inner hair cell loss, which is what directly synapses with the auditory nerve, so it takes a signal and kind of translates it to the nerve. And when we were talking about cochlear synaptopathy, which is basically a problem with the synapses in the cochlea, and the synapses as a nerve connection, that's the inner hair cell connecting to the ganglion that ultimately leads to the auditory nerve.

**Hazel:** Alright. So they clarified that their drug targets both the inner and outer hair cells.

**FGG:** Yes.

**Hazel:** Why was it important for you to understand that and what does it mean, if only one or the other is targeted? What is the difference in terms of the result that one would experience?

**FGG:** Well especially for tinnitus, they don't know whether it's individual, whether it's an outer hair cell or inner hair cell problem. They know the signal at some point is disrupted. And whether knowing what's damaged if it, say, only worked on outer hair cells and you add inner hair cell damage, you may not get the results that you want.

In terms of hearing, when you have inner hair cell loss that contributes to things like speech in noise difficulties, because you don't have the normal connection with that synapse. They're still working out exactly what each component does in terms of its contribution to hearing, but inner hair cells transmit the signal, so you definitely need it functioning for normal hearing. So, it's important too.

**Hazel:** Carl also talked quite a bit about the importance of clarity of hearing, and this seemed to imply that, you know, rather than using traditional hearing tests, it's better to use some kind of test that actually measures how well someone can hear in different types of situations, and how well they can make out speech. Why is that important, and why are the traditional tests not suited for that?

**FGG:** Well, the traditional tests only go up to 8,000 Hz, which is kind of based on the fact that hearing aids cover that range. So that's traditionally where they stopped, because that's the only treatment for hearing loss. So, there wasn't really a value, at least therapeutically, in testing for more. But, as he pointed out, the difference between 'chore' and 'shore' when

you're doing the word score does depend on higher frequencies as well, and so they're taking the initiative to measure them, because they think they have a drug that targets those very, very well.

**Hazel:** Is this what they mean when they talk about 'hidden hearing loss'? Or is that something else?

**FGG:** That's something else. So, this is word score. Hidden hearing loss is 'speech in noise' difficulty classically. Although people use the term in different ways, but classically it is what they call cochlear synaptopathy, which is a condition where you have connections, but you have less of them than you should, which makes it harder to filter out unwanted noise and hear clearly.

**Hazel:** And I believe that also has to do with the auditory nerve and not just the hair cells, correct?

**FGG:** It has to do with the inner hair cell connection to the nerve, to the spiral ganglion. So, kind of both. But what he was saying is that, potentially, when you regenerate the inner hair cell, those connections, just like when you're in the third trimester, start to reform. And, say, you have an inner hair cell damage problem, you can regenerate that hair cell and thus regenerate the neural connections. So, in those specific situations it can also help cochlear synaptopathy.

**Hazel:** Great, thanks FGG, for explaining all that so clearly. Was there anything that you heard during the interview that you found particularly interesting?

**FGG:** I liked hearing that they had maybe some anecdotes for tinnitus. Because I know that they don't – they weren't measuring it in Phase I, so they didn't have the hard data. But just knowing they had maybe testimonials is very heartening for sure.

The thing that I guess meant the most to me were two things: One is that ototoxicity was not excluded, which of course in my case was very good to hear. I'm hanging on a thread, hoping for something that will help. And that was very, very important to me personally, obviously. And then in general, the compassionate use answer was really important, the fact that they're willing to revisit that based on the Phase II data was really wonderful to hear, because, you know, it means that they are interested in getting this out to people, helping people as quickly as possible. Especially for people that may not qualify for the trials, you know. Of course, emotionally, I just want to get anything that will help as soon as possible, and just knowing that there's something that I can try that maybe, maybe it's available soon. That was very good to hear.

**Hazel:** Yeah, I'm sure that sentiment is shared by many. Well, I want to thank you so much for making the trip. I understood you drove 8 hours to be able to join us.

**FGG:** 8 hours, yeah.

**Hazel:** Yeah, in spite of your struggles with tinnitus and I believe also visual snow.

**FGG:** Yeah.

**Hazel:** Yeah, thank you so much.

**FGG:** You're welcome, I'm glad I could do it.

**Hazel:** And thank you also for explaining us some of the technical bits, for those of us, including myself, who are less informed on such matters.

**FGG:** Of course, you know, I hope that was clear.