Steve: Do you believe that regenerating hearing will actually resolve tinnitus?

Marcelo: Probably yes, it will have a very positive impact.

00:08 – Introduction

Sean: Welcome to Tinnitus Talk. Today we're discussing a topic that many of you have been waiting for: hearing regeneration. It's a topic that's much hyped on the Tinnitus Talk support forum; we've received loads of requests to make a dedicated podcast episode on this.

It took us a while to find the right person to interview, but luckily we found **Professor Marcelo Rivolta**, from **Sheffield University** in the UK, who's an expert on stem cells and their application for hearing regeneration. He's great at explaining this very complicated topic in layman's terms, so even if you're not deep into the research yourself, give it a try because this is fascinating science.

We want to thank **David Stockdale**, from the **British Tinnitus Association**, for facilitating this interview. He put us in touch with Marcelo, and he also conducted the interview on site in Sheffield, together with our Tinnitus Talk member and former director **Steve Harrison**.

I want to thank all of our – so far – eleven Patreon supporters! You're enabling us to continue to produce this podcast! Please visit us on tinnitustalk.com/podcast for information on supporting us, or to provide your feedback, we're always happy to hear from you.

Now, I won't detain you any longer. I hope you enjoy this episode!

01:23 – Introduction to Stem Cells

Steve: Hello and welcome to the latest edition of the **Tinnitus Talk Podcast**. With me today interviewing is **David Stockdale** of the **BTA,** and we are interviewing **Marcelo Rivolta,** who is from **The University of Sheffield** and a specialist in hearing regeneration.

Hello Marcelo.

Marcelo: Hello Steve.

Steve: Firstly, can you give us a little bit about your education and background in research?

Marcelo: Sure, I originally trained as a medical doctor, as a physician, and very early on in my career I moved out of clinical work and I concentrated on doing lab work, so fundamentally a scientist. But I have a medical background, which is pretty useful in this case and I then made a career in academia and I am now a **Professor of Sensory Stem Cell Biology** here at the **University of Sheffield**.

Steve: Excellent, so what sort of background do you have in stem cell and hearing generation research? What sort of projects have you worked on to date?

Marcelo: Ok, for a number of years now we have been working with human stem cells and, particularly, with a type of stem cell which is called a **'pluripotent stem cell'**. There are two 'flavours' of this type of stem cell. One is called **'embryonic'** because it is taken from very early stage embryos, and the other one is called **'induced pluripotent'** and that is a technology that basically allows you to turn any cell of the body, like a cell from the skin, into these pluripotent stem cells. Pluripotent means that if you are giving the cells the right instructions you can make them produce any cell type of the body, and what we have done in our work is develop techniques and methods to produce ear cells out of these purely pluripotent stem cells.

David: So, what does that mean?!!

Marcelo: Well, it means that if you are thinking about regenerating and repairing an organ like the ear which has very little, if no, capacity at all, to repair itself then you need to produce the right building blocks, the right bricks, to repair the ear. And those bricks, those building blocks, are these cells that you produce with stem cells. So, we have done that in the lab and then we have put it into a model of hearing loss, into the animal we use, which is a gerbil. The reason we use a gerbil is because the hearing of the gerbil is very similar to human hearing. It's closer than mice or rats, for example. We put it in a gerbil that was deaf and the type of deafness that he has is where it is the nerve that is damaged, particularly, and we saw that the cells integrated and they produced a functional recovery. So that is the kind of the **'Proof of Concept'** or **'Proof of Principle'** that we have done by using stem cells to do this kind of repair and regeneration.

David: So, what would be the next steps for that work and how would you take it forward?

Marcelo: Yes, specifically for this work there is a series of things we need to do. We need to show that the cells themselves are safe, because obviously when you are dealing with stem

cells, particularly when you are dealing with these pluripotent cells which can do a lot of different things, you need to make sure that they will not produce tumours. One way of doing that, first and foremost, is to make sure that these undifferentiated cells are no longer in the mix; that you put only the cells that are already programmed to be an ear cell, but also that you test this in different ways in the lab and in animal models. So, I have to say, so far these are still things that are happening but, so far, we haven't seen any concern or any problem. And, also, we need to evaluate other things about the cells. For example, the resilience long term of these transplants and things of that sort. Everything that we are doing is sort of with the idea of, in the near future, being able to go into a real target population, which is human patients, basically.

David: I was going to say that some of that must be quite long term by its nature, basically, to check that this doesn't turn into a tumour and to check that it's safe.

Marcelo: Yes, exactly, exactly, and that's why all this research takes a long time to do and we want to be very thorough and very careful and very certain that when we get there that we get there with all the right tools. I know sometimes if you are suffering from this condition then there is an anxiety to say: 'why is the research not moving faster, why don't we hear faster?', but we have to be sure that we get there at the right time with the right information and that's why it takes time to get there.

Steve: So, in terms of the safety profile, how far off, if you could give an estimate, do you think it is from having the correct safety profile to look at human trials?

Marcelo: There are different levels in the way that you handle that. There is one level that you kind of do it in a research context and then you have to move it on to an industrial manufacturing kind of context, but I would say we are hoping that in the region of maybe three or four years we could start with a clinical trial. Let's bear in mind that a clinical trial doesn't mean that you are going to be able to go to your doctor and say 'I want this drug to put in my ears'. Clinical trials are still research. It is still research but under very controlled conditions in a hospital which has a very strict protocol, you are seeing patients. But it is still research. But it is a very important step, because you are trying now this in the right population, in the right group of people – the patients basically. It is no more in the lab.

07:20 – Targeting the Correct Area with Stem Cells

David: Something I've always really struggled to understand a little bit when we're talking about hair cell regeneration within the cochlea is: how do you know you are going to target the right area where there is hearing loss, because there are lots of different hair cells and lots of different connections. How do you know to target the area?

Marcelo: Yes, that is still a challenging point. The way that we approach this is, at this moment our initial target is that we're not going for the hair cells. We're going for the nerve. We are going for what's called **'neuropathic deafness'**. We are trying to replace the cable that connects the hair cells with the brain. The hair cells are something that we hope to target in the future but, at the moment, it's far more challenging. One of the reasons is because it is very difficult to get to the place where the hair cells are, so, surgically. But I think the

technology and the research that we do and that we are developing, we hope will allow us to make that leap quicker once we get everything established for the nerves and for that we already have nice data from the animal models.

Steve: So, this would be the synaptic connection which is what is often referred to as **'hidden hearing loss'** that you target?

Marcelo: Yes, yes, in a way. I fear hearing loss is a little more complex than that. Hearing loss is a range of conditions or problems that can often go from just the loss of the synapses but you still have a neuron and you still have a hair cell and basically the loss is just a connection to, in the most severe of cases, a complete disappearance of the fibres and of the neurons. So, what we think we are going to be targeting is when most of the neurons are gone, rather than just the connection, the synapses, which is one of the things underlying hidden hearing loss.

Steve: Yes, because I think I remember, I think it was from a **TRI** talk by, was it, **Charles Liebermann?** When they said was it 95% degradation before you actually notice it in your hearing?

Marcelo: Yes, the thing that is very poignant and a point that is important to take about hidden hearing loss is that the nerve has always been seen as, 'well, it's not as important. The hair cell is everything', and what **Charles Liebermann's** research shows is that the nerve is very important and, also, is probably the first hit, the first thing that it drops is the nerve and then you start seeing all sorts of other problems. It's changing a little bit the way we are looking at the problem.

Steve: So, effectively, I think we've got to remember that the nerve is the first thing that gets damaged as well. It the most damaged.

Marcelo: Exactly, exactly and traditionally we always thought that it was the hair cell that first gets damaged and then the nerves sort of, as a consequence, but that kind of research, that kind of data, is starting the show that the nerve can be a primary target in its own right and you can lose neurons before tending to lose hair cells.

David: And I mean we're touching on broader research in the area of hearing regeneration as well. I mean, is there anything beyond the **University of Sheffield** that's happening in the field at the moment that really excites you?

Marcelo: Yes, I think in the last few years we have seen kind of a revolution of things coming together from different disciplines into our field. Specifically, in the regeneration field within hearing research the other things which look quite promising as well. There has been a bit of a movement in regard to gene therapy and also the use of some small molecules, they are little drugs from a pharmacological agent where the idea is that it could do some sort of internal repair. The problem is, at the moment - although there is data supporting some of these strategies - it is very early days for all these therapies and because there are different ways of producing deafness I think it is very interesting to explore these other things and see which one will deliver and produce the right answer. And probably, in the end, it won't be

just one strategy, it will be a combination of strategies or different strategies for different problems.

11:41 – Types of Hearing Loss, and How Much Can be Recovered

David: So, it's almost like we need to sub-type hearing loss more effectively first, as well?

Marcelo: Yes, with hearing loss we tend to talk about deafness or hearing loss as a single entity, but it's not a single entity. It has different causes, different parts of the ear which get affected and these different strategies will need to be targeted in a slightly different way.

David: So, I guess a challenge once we start to understand these potential ways to regenerate hearing better, is to have better diagnostics for hearing loss as well?

Marcelo: Better diagnostics, better ways of measuring the functionality of different parts of the ear are certainly something which is very important.

David: I mean, we are talking about it already, but are there different types of hearing loss that you think are better candidates for hearing regeneration? I know that, obviously, there is the neuropathic.

Marcelo: We think for example for the cellular approach, neuropathic deafness is probably a much better candidate because the nerve is more accessible, and, as we have shown in **Proof of Concept,** it can be done. The hair cell remains the main target, the main aim but it is still very, very challenging to get there. There are other cells that can fail within the ear which conceivably could be targeted with a cell therapy approach. I think is what makes the cell therapy approach quite exciting and robust, is that if you are going to replace a molecule you need the whole architecture there. You need the whole cells in place but if you don't have the cells in place you need to start from scratch and that is where the stem cell therapy really comes into action. You could, conceptually, replace different cell types with cells that you have produced in the test tube.

David: Because there are 'dormant' hair cells within the ear, is that correct?

Marcelo: Well, not 'dormant'. They are not dormant hair cells. The idea from people that would like to use a molecule or a drug is that they expect that it would be cells in the ear, dormant kind of stem cells, cells which can be recruited and be pushed to become a hair cell, for example. The problem is that a lot of evidence, a lot of work has been done in that area and it's not really clear that there is such a thing. There are certain approaches, so they look a little bit more promising, but they have been tested, mostly in the test-tube. It has been tested with cells outside the right environment, but when you test them in the animal, particularly in a mature, old animal, it's not that straightforward. But that is the hope as in the way that other organs have these kinds of dormant stem cells, they may have but it's not clear that it does.

Steve: So, we really are thinking that, in your opinion, regeneration of hair cells is going to be the key thing. Do you believe that a regeneration of the cells will be degraded from the initial,

so when you've got 100% would the hair cells be sort of 50% if the regeneration happens, or will it be closer to 100%?

Marcelo: I think it will probably be a gradual recovery. It will be really, really, amazing if you could get 100% recovery but also because the whole system, with normal wear and tear, with normal ageing, starts to fall apart in a way. What we aspire to achieve, initially at least, is a recovery of such magnitude that it would be meaningful for the normal functioning of the individual but expecting a complete, 100% recovery from day zero, I think that would probably be very, very unlikely. For example, in our strategy we have seen in the model of neuropathy is a recovery of about 45 – 50%, which translates from the recovery from Db's is substantial enough to go from being profoundly deaf to having a kind of deafness, or a hearing that will allow you to maintain a conversation in a room, for example. So, it has that kind of implication in real life but it's not 100% recovery.

Steve: So, do you think that it will be in the regeneration scenario that the hearing would just come back, or do you think that there would be an element of re-learning in the brain when the hair cells come back?

Marcelo: That's a good question. It all depends, I think, on how quickly, how early we can try to implement the therapy that we are talking about and, also, if it is a patient that has been completely deaf since birth or from early childhood, or it's something that has been acquired later in life, because obviously the brain will have to re-learn and become more plastic, but it is a question that mostly still remains unanswered, because we haven't explored that much with the type of regeneration.

17:05 – From Animal to Human Models

David: So, changing gear a little bit, whenever I've read or seen anything about hearing regeneration, it's often related to different animal models. So, we know, for instance, different species of birds can regenerate their hearing. Is there any work going on to learn from what we know already exists in the animal kingdom and seeing if it's something we can apply to humans?

Marcelo: Absolutely, absolutely! And you've brought up a very, very good point. The initial work showing that birds can regenerate was done in the mid-80s, primarily by **Ed Rubel's** lab and independent researchers in the US, so about 1984/1986 if I remember correctly. So, for the last maybe 30 years we have been having a lot of research comparing these models and we have learnt a lot. In particular, a lot of the molecules which birds use to regenerate their cells are similar to the ones that are involved during normal development when the ear is being formed. However, it has to really identify something that would clearly touch and make the human, or mammalian, ear more like a bird's one, but there's been a lot of research and it was, and it still is, a very exciting area of investigation because of the analogies and the similarities that you can try to extrapolate.

David: So, it's a sort of 'watch this space' really? We know what it can do but we're not quite sure.

Marcelo: Yes, but the thing is it's been going on for a while. It's not something new.

Steve: So, is one of the impediments, maybe, that it's not as sophisticated for the hearing in birds?

Marcelo: I don't like to use the word 'sophisticated'. Because I think the birds have a very sophisticated ear anyway, but it's true that the anatomy and structure is simpler and when you look at the structure of the cochlear, the mammalian cochlear, it's such precision, it is such a fantastic piece of engineering, such a precise piece of bio-engineering. It is kind of where the idea that we put forward in the past is the reason why the system cannot repair is because it is so complex, and once it's built you want to keep it as it is and you have lost this kind of ability to regenerate it through evolution, basically.

19:17 – How can Stem Cells Treat Hearing Loss?

Steve: So, slightly aside from that. Thinking about stem cells can you explain, or is it possible to explain, how stem cells can potentially treat hearing loss?

Marcelo: One way, that they could do – it's what we are trying to drive – is, once you understand how to work with, particularly with these very plastic pluripotent stem cells … because a stem cell is basically a cell that is like a white canvass. It is open to instructions and to produce anything that you give it the instruction to make. That is why these induced pluripotent stem cells are very attractive, because the cells can be taken from the same patient, you reset them, you re-programme them to become a white canvass and then you give them the instruction to be the cells that you want them to be and, in this way, you can generate the specific cell type for the ear and you can have different, what we call protocols, different recipes, to produce a hair cell or an inner hair cell even or an outer hair cell or a spiral ganglion neuron or whatever, and then you make those cells in the lab, in the test tube and then you transplant them and you use that as a therapy.

The alternative vision of the target use of the stem cells, rather than going with something you produce ex vivo, that you produce outside of the body, is trying to awaken these endogenous cells that we were talking about. The problem is it's not clear that those cells are really in the mature cochlea or they are very, very refractory for these kind of instructions to be pulled back, but that is generally speaking, that is the other strategy, trying to see if you can target any sort of endogenous population of stem cells and push them to become the right cell type that you want.

Steve: What sort of stage is that research at, at the moment?

Marcelo: Do you mean endogenous cells?

Steve: Both.

Marcelo: Both… well, using the outside cells is something that it is, in these days, I would say, pre-clinical phase but trying, moving forward to clinical trials is the kind of thing that we are trying to do. The other strategy is also quite advanced in a similar thing. I think at this moment

there are a couple of examples which are a little bit more advanced. They are taking it into clinical trials already and we have to watch this space and see what is going on. It's an open question at the moment.

21:46 – Ongoing Clinical Trials

David: So, is that the **'Regain'** Trial that is happening at **UCL**?

Marcelo: **Regain**, yes, that's one of them. The other trial is the one supported by **Frequency Therapeutics**, which is kind of a different compound, different molecules, but sort of similar principle, sort of trying to recruit endogenous cells and see if they make the switch.

David: And, so, both of those are delivered via injection only, intra-tympanically, through the tympanic nerve? It's interesting, I was speaking to someone on the **Regain Trial** at a **UCLH** event and he was describing what happened in a really interesting way. He was saying maybe that type of therapy will almost become like having an operation on your eyes, so you don't need glasses. It could almost be that you know you use a hearing aid, and that's ok for most people but, actually, if you want to go to that extra level then you could have that sort of treatment to actually regenerate your hearing and I thought that was an interesting way of viewing it, which I've never thought of before really.

Marcelo: Yes, if that works, it's very attractive. Obviously, having an injection through the tympanic membrane - the problem is it probably means that the different compounds, different drugs reach the ear in different ways and, for some things, you need to put the material or the cells or the drug in the right place so the tympanic injection is very good for things like you want certainly to deliver to the middle ear, which is the intermediate cavity where you have the little ossicles; and some compounds go all the way into the inner ear. But how efficiently they get there and how specific they can be… so, yes, it's an exciting idea, the possibility of having a very short intervention and an injection and, yes, off you go, but it is still far from being proven.

Steve: So, the delivery method could be absolutely as important as the actual treatment itself?

Marcelo: Yes, it will be very important, and it will probably be combined with the agent that you deliver being this molecule, a gene therapy like a viral particle, or cells, whatever you want to deliver.

David: I think here it just shows how many moving parts are needed to come together to show that this type of research is going to work as well. Because I know another very fertile area of hearing research at the moment is how you can have different ways to administer drugs further and further into the ear and have a longer life whilst they're there to have some sort of action as well. So, again, that's needed it feels as well.

Marcelo: Absolutely, absolutely. It has advanced a lot lately but still a lot more work needs to be done.

24:21 – Success Factors for Hearing Restoration

Steve: Just thinking back to about to when we were thinking about regeneration therapy and the impact it can have, you know, how much hearing you can get back. Do you believe it will be limited in frequency range or will it be across the whole hearing range?

Marcelo: Again, that is not completely clear. It may depend on the type of therapy or the approach that you follow. For example, what we have seen with cells, are that the best areas are the ones closer to the place that you inject or the more basal part of the cochlear, but you have recovery all across as well. But that could vary depending on delivery and type of delivery and type of background condition as well.

Steve: Were you able to do any testing of frequencies in the gerbil model?

Marcelo: Yes, yes, and that is the test I am referring to, so you particularly get this kind of mid- to high-frequency range, but you can see a trend at least of a recovery in the other frequencies as well. So, they seem to take cues from the environment and find their way.

Steve: So, it's almost in tandem with the mid-ranges where we actually need it?

Marcelo: Yes, absolutely, absolutely. Which if you are going for the base of the cochlear it's closer to the target as well.

David: So, any other known factors such as age, or time elapsed since noise exposure that could influence the success of hearing restoration?

Marcelo: Yes, potentially, those factors are going to have an impact, and it is likely that a system that is very young and is still plastic will react in a different way to a system that is more mature and what happens where it has been set and also that, when longer time has passed from the initial, particularly if there is an unidentifiable cause, like an ototoxic drug or something that may have happened in the past, that may have an impact. We have explored that a little bit in our system but not very, very long term but the conditions that we have explored don't seem to be having a very obvious consequence. But they are still like in the more short-term kind of damage. But the long term… probably… for example, there was some work now at a clinical level on the use of a virus for the induction of '801', which is a gene that will drive, in theory, the conversion of the hair cells and that type of strategy seemed to be very, very dependent on the time of injury because the genes seems to be doing the trick, making the switch, only when the cells, what are called the supporting cells, are very receptive, very competent to do the act. If you let the time pass a little bit longer, those cells change and then they will not be receptive to do the resetting of the hair cell.

David: So, some of that, I know, is slightly different but it is almost linked, to what we know about using a hearing aid or assisting with hearing now, that the longer you leave it, the harder it is to take action.

Marcelo: Yes, and that probably is also to do with the case of the hearing aid and the prosthetic devices with the rest of the pathways. I think we were talking before about being less plastic, the central auditory pathway.

David: What you say about hearing loss after ototoxicity is interesting as well, as I guess that opens a very straightforward pathway to test some of this really and I guess this is a potential way to give insult and it's creating that hearing loss, so therefore something you can test in a very robust way?

Marcelo: The use of ototoxic drugs is a very commonly used model, at least in the research environment. It's been explored also in the clinical setting but in a clinical setting it is more used for the development of oto-protection which is the other area where there is a lot of activity of different groups trying to develop drugs that you can administer with non-ototoxic drugs, for example, antibiotics, or chemotherapy drugs and trying to minimise the damage that these drugs are known to cause. But that's a different story. It's more oto-protection rather than regeneration as such.

27:40 – Experimental Treatments: Platelet Rich Plasma Injections

Steve: So, one thing that has been a popular topic on the **Tinnitus Talk Forum** is, what are you aware of and what do you know about the efficacy of platelet rich plasma injections into the tympanic membrane as a regenerative treatment?

Marcelo: I am not very aware of any kind of…. I think I have seen a single paper when they have explored that 'in vitro'. Again, in a test tube. And they have some interesting ideas, but I haven't seen any data from an animal model, from any sort of impact or effect. I know that, I think it has even, in a certain part of the world, been offered as a treatment and I have to say I haven't seen any data published or communicated in conferences that would support that strategy. It's probably a little bit premature at this stage.

Steve: Something in development effectively, a 'watch this space' sort of thing?

Marcelo: Yes, but it's always a little bit of a concern if it's been applied sort of clinically without a bulk of evidence. It's what we were saying before. All these developments take quite a bit of work in the lab and then you do the transition to a different stage, so you have to have the bulk of evidence to support that.

David: And you'd want to see the safety data as well, I guess. Do we know if that exists at the moment?

Marcelo: I haven't seen anything regarding that type of therapy, no.

David: Are there any reasons why injections of stem cells would be dangerous or unwise into the ear?

Marcelo: There is always the concern because it is a new therapy. It Is a new thing that is going to be tried in the year, but we said we are developing and are doing a lot of the right

tests under the right controls and we are, in a way, in a very nice scenario because although it hasn't been done in the ear, there are people who have been trying similar types of stem cell therapy in other fields. For example, the eye, in macular degeneration. There have been also some developments for conditions like **Parkinson's** at a clinical level, and none of these studies have shown any kind of adverse effect or side effect that would concern us but, obviously, we have to be careful and we are doing all the right sort of controls and experiments to control and minimise that.

31:32 – Will Hearing Regeneration Resolve Tinnitus?

Steve: I guess what you'd call a million-dollar question. I think we said, I don't know if we mentioned it, actually, you are not an expert in tinnitus, but you operate around that field of research. Do you believe that regenerating hearing will actually resolve tinnitus?

Marcelo: It's very important to emphasise that I'm not an expert in tinnitus. I don't directly work in tinnitus, so don't hold me to account on this. But I am in the area, I am in the field and I would say, probably, yes, in the sense that tinnitus, as you know very well, is a very complex condition and it is produced by problems at different levels in the pathway, but one of the things which has a very close association is the damage of the auditory organ and it is very closely linked to hearing loss. So, we think that if hearing loss can be repaired biologically, and you have a way of kind of resetting and controlling the input into the auditory system, then it could have a very positive impact in tinnitus. But again, if it is a different type of tinnitus, it may help some but not others, and it has that kind of uncertainty as well but I think, on the whole, and if you ask me for a very simplistic answer, I would say, probably, yes. It will have a positive impact.

David: So, from what you said, it's going to have a positive impact I guess where the causation is something auditory-related or where it has something to do with the hearing.

Marcelo: Yes, it will be different if it is more central and if there are other paths affected basically.

33:06 – Getting to Market

David: So, looking at what else is happening in the wider field? We have spoken a little bit about why the pace is slow. I mean, what trials do you see progressing? Where do you think we will see the next in human trials of some of the therapies that we have discussed?

Marcelo: Do you mean, where are we going to see them specifically in the type of trial? The type of agent?

David: Yes, just a little bit of speculation, I guess. But you know, which ones do we think are promising and looking as though they are going along the pathway at a reasonable speed?

Marcelo: I think probably we are going to see in trials in the three different disciplines. I think we're going to see trials in the gene therapy area, using viral **vectors (?)** to deliver genes and that particular type of trial will have two types of work. One which is targeting a very specific

genetic condition, so you have a deficiency in the gene, and you are trying to replace that gene with a healthy version and, hopefully, targeting problems that have what is called 'a late onset'. So, if the gene sort of falls apart by the age of 25, then you have a nice window of treating that patient before that. But it's very specific: that group, that gene, that particular problem.

Then with gene therapy there is this idea about these kinds of genes like 801 where you could trigger that and use it for regeneration but we discussed that, that it is dependent on also having the right cells receiving that gene but I think there will be trials. There is one already going on at least and there will be more coming from that space. Molecules there will be also investigation. Most of the stuff that will come probably will be more about oto-protection and then we hope we will be able to drive also the cell therapy angle and see cell replacement into the clinic or into the clinical trials.

David: So, different things happening, really?

Marcelo: Yes, different strategies, different flavours.

Steve: So, we talked a little bit earlier about where you are in terms of the safety profiling and moving to the next stage. How long, in your opinion, do you think it will it be before we've actually got things coming to market and which will be widely available?

Marcelo: That's very difficult to say because we don't know, but we hope that everything will go really well during the clinical trials but that could be another sort of area where things may expand and take longer, but assuming that everything goes to plan considering the time that we need to get into the Phase 1 2A sort of Trial and then moving into Phase 2 and Phase 3, we think probably, maybe in the region of maybe 8 – 10 years until something could be available in the market.

David: How much do you think it will cost as well because, you know, that's another level on this isn't it. I don't know if it's possible to say at the moment.

Marcelo: It is very difficult to predict at this stage, but on the general wide view even if something is very costly initially, we have examples of other technologies where the technology gets better and more efficient and the cost goes down and it becomes more affordable but it is a very complex sort of calculation, so it's really very, very difficult for me to do any sort of estimate on that.

David: Especially because we don't quite know what healthcare will look like in 8 to 10 years anyway so, yes, maybe other things have moved on too. I mean, linked to that this feels at the moment like quite an active field, a number of Universities, a number of biotech companies really active in this space. Can you say anything about the different sources of funding available at the moment? Do you think there is enough money there to really keep this going at the pace it is needed?

Marcelo: Well, unfortunately, probably not. In the sense that there is money out there. The public funds have been supporting this kind of research, charities have been supporting this

kind of work, but the problem is on the public front you are always competing with conditions which are perceived as a far larger priority. If you have a condition which is life-threatening, for example, when you go to a Medical Research Council discussion you have to compete with severe neurodegeneration, with cardio-vascular conditions, with cancer. So, hearing loss has always been in that kind of situation, which is like, yes, ok, it's important but it's not at that level so that makes the competition more difficult. The industrial investment has always been very, very challenging but I think we have seen now in the last few years a new interest and the industry is coming into this space because they see the potential and they see that not much has been done. But there are a lot of things coming in the pipeline and, in that sense I think it is very nice scenario and very optimistic But if you go, particularly when you want to take something to what we call 'Blue Sky Research', and you have an idea and you want to explore it but it could be revolutionary or it could fail tomorrow and it's something very, very new. That kind of research, fundamental research is quite difficult to get the right funding.

David: To me, for someone who's been around tinnitus and hearing loss research for the last ten years it feels especially in the last three to five years the pharmacological and the hearing regeneration research, in particular, has really sophisticated and matured a lot. It does feel like there's been a lot of progress made and it now feels like it's almost at that stage where the major investment is needed for those big trials to really push it into in humans, it's megabucks I guess, isn't it? It's big amounts of money that's needed for that.

Marcelo: Yes, absolutely.

Steve: It seem that recently you've got a research grant, haven't you?

Marcelo: Yes, we've got a research grant from different bodies but also we are very excited because very recently we managed to **spin out** a biotechnology company from the **University of Sheffield** with support from different industrial investors and it's something which we are really, really excited about because we think it is a way of being able to take this all the way into the clinical trial, into the patient. Because as we were saying before, trying to do that with conventional funding streams, would be very difficult, if not impossible, because even funding streams from the conventional Research Councils want to see what are your plans or how this will go all the way, because at some point they need to basically let it go. I think we are very happy now that we have just spun out our company, which is called **Rinri,** and our aim is trying to develop stem cell therapies for the treatment of hearing loss.

Steve: Excellent. That's something that is vitally important because you are much more open to private funding and you can roll out the company and really push the research forward.

Marcelo: Absolutely, absolutely.

David: Congratulations on that as well because it looks like you have significant funding to start it off. So, what should be the first things that we should look for from Rinri? What are the sort of signs that we will see that it's succeeding in the trials?

Marcelo: Well, we are doing a bit of the pre-clinical work that we'll need to take us to the trial and then we are hoping to be able to get into the trials. So, hopefully, you will hear from us

and everything will go well. It's early to say, but that's our aim and we're working really hard to get there.

David: Excellent, and we really look forward to following your progress as well.

Marcelo: Thank you.

Steve: So, for the listeners is there a website available now? Something where people can keep up to speed?

Marcelo: All this is very, very new so we have a very sort of basic website at the moment. If you Google:

https://rinri-therapeutics.com/

it will take you to an initial portal, but we are hoping to develop and to establish this in the next few months so you will have more information there.

Steve: Thank you very much Marcelo. That's absolutely fantastic. We've definitely learnt a lot during the time we've being doing that. A lot of information I think for the listeners to take in as well. Thank you very much for appearing and, thank you as well, David, for co-hosting.

Marcelo: Thank you very much for the invitation. I'm very happy to be here to have the opportunity to explain a little bit what we're doing in the lab and, hopefully, you'll have some exciting news in the near future from us.

David: Thank you. It's really exciting to run through what's happening in hearing regeneration and I think there's real hope for people living with tinnitus that there may be something there for them too.

Marcelo: Absolutely, thank you!

42:03 – Behind the Scenes with Markku and Hazel

Markku: Wow, we were just so lucky to hear about Professor Rivolta's cutting edge research! We hope you too enjoyed this episode.

I'm here with Hazel, our director, to briefly talk about this podcast, why we are doing it, what our plans are. So, if you are interested in a behind the scenes look, keep listening. If not, well, you're excused.

Hazel, before we talk about the podcast, can I just ask you about your impressions of the Marcello interview?

Hazel: Yeah of course. I have to admit it's a new topic for me, but I learned a lot. We just felt we had to do an episode on this topic, because we got a lot of requests. We have some

members who feel very strongly about this topic and believe this is where the solution to tinnitus will come from.

The field of hearing regeneration has exploded in the past few years. There are different approaches like stem cells and gene therapy, and also different ways to target hearing regeneration; you can target the damaged hair cells in the cochlea, or the nerve that connects the ear to the brain; Marcelo seemed to feel that is a more promising avenue. I learned a lot.

I also heard him say that it might be 8-10 years before we'll see something on the market, which seems a long time, and part of me wonders whether even that is optimistic, I don't know. But of course, we do have clinical trials going on, they were mentioned during the interview: **Frequency Therapeutics** and **Regain**. So hopefully those will pan out and we'll see something on the market soon.

In the meantime, we also know there are already experimental treatments offered in certain countries. For instance, a couple of members of the Tinnitus Talk forum have travelled to South Korea to get PRP, that's **Platelet Rich Plasma**, injections in the ear. I wouldn't per se recommend anyone else to do that, since it's experimental, but it does show that when people are desperate enough – and of course tinnitus can make you very desperate – people will go to great trouble and expense and pretty much try anything.

Markku: Yeah, I agree. And I still see today – less and less, but still – funding going into mindfulness and CBT studies, and I think we should start to completely focus on treatments that effectively treat tinnitus, reduce the volume, reduce the intrusiveness, instead of these psychological approaches. And what these experimental treatments in South Korea tell me is that tinnitus is so much more than just a noise or a little nuisance to millions of people in the world. And when there are two options, a very dark option when you've lost so much to this condition; you might have lost your job, your family, your social relations – then you're willing to attempt these experimental treatments. Overall, we need more research into effective treatments, and I hope tinnitus organisations will start to focus solely on the cure aspects.

Hazel: Absolutely. So I want to move on to discuss the podcast. And I wanted to ask you, Markku, what inspired you to start it? A bit of background for the listeners: You created **Tinnitus Talk**, the online support forum, eight years ago, and have worked on it tirelessly since, and have done so much for the tinnitus community. Why did you also want to do a podcast?

Markku: Well, the podcast originally was mine and Steve's idea. Steve interviewed **Will Sedley**, a UK based researcher. We never published that one, but then late last year one of our Tinnitus Talk Forum members, **Jack Straw (aka Sean)** came up with the idea for a podcast, and we said we already recorded an episode but would like to create a series. And he has such a good radio voice and is so enthusiastic, one of our best volunteers really, so we said of course we'll go with this and see what comes of it. And because we have contacts in the research community and a wide network of people that we could interview, we thought we could bring those experiences, both from the research side and what goes on in tinnitus management, to the listeners. I'm really happy we got this off the ground and look forward to many more episodes in the future.

Hazel: Yeah, same here. What are your feelings about the podcast so far, has it met your expectations?

Markku: It's a LOT more work than we thought! I think you added up the hours and came to 70-80 hours per episode. That seems ridiculous to others probably. But the amount of work that goes into planning, contacting the people, often you have to do test recordings to test their equipment, coming up with the questions, asking our members, curating those questions, sending them to the interviewees … Then you have the actual recording, and then you have to edit it – that takes quite a bit of time to edit it properly, to make it sound nice and remove all the unnecessary bits. And then you have to publish it, create all these text snippets and graphics and put everything on **tinnitustalk.com/podcast** and create a thread on the forum. It's a lot of work and I hope people appreciate this.

But also, the response has been way better than we had imagined. We've had about 25,000 listeners per episode, and this has far exceeded our expectations. We're very happy that we have this significant group of people listening to our episodes.

Hazel, you've been following closely the reactions to our podcast and engaging with listeners online. How do you feel about this? Have the responses been mostly negative or positive?

Hazel: Yeah, I've been doing some follow-up after each episode, engaging with listeners on our forum and the various Facebook groups. So far, it's been overwhelmingly positive, people are happy we're doing this, no one has said "I hate the podcast" or anything like that. But not every episode will appeal to every listener. There's a group of listeners out there for instance who only want to hear about research and not about management, so they won't like episodes that are not about research. You can't always please everyone, and I guess we're trying to appeal to a broad audience. So far, we've only been able to cover a few topics, but we aim to cover a lot more and let the listeners' responses inform what we cover.

Markku: Let's talk a little bit about future episodes, just to follow up with what we have in the cards in terms of guests and so forth. What's in the pipeline?

Hazel: There are actually a few episodes in the pipeline that have already been recorded but we still have to edit and publish them. I interviewed two of the co-authors of the new **European Clinical Practice Guidelines for Tinnitus**.

Markku: Let me cut you there. Because we had an issue with that episode specifically. We struggled with it, because the audio quality is low. I worked on that tirelessly for 30-40 hours. So we will see if we can publish it, because the quality is low in my opinion. But maybe the content is worthwhile.

Hazel: True, Markku has very high-quality standards.

We did an interview with the chief scientific officer of **Cognosetta**, a small drug development company that is trying to develop a drug for tinnitus.

And I interviewed, while I was in Taipei for the **Tinnitus Research Initiative (TRI)** conference, I interviewed the scientific coordinator of TRI, **Winfried Schlee**. We talked mainly about how we can involve patients more in research, a topic that we feel very strongly about.

So those are three episodes that were already recorded and are coming out, and then there are quite a few people who've tentatively agreed, but we still have to schedule something and record it:

- Most likely, we'll have someone of from **Hearing Health Foundation**, also talking about hearing regeneration. So in a way our "hearing regeneration, part 2" episode.
- We'll be interviewing **Bryan Pollard**, president of **Hyperacusis Research**, to really do an episode dedicated to hyperacusis.
- **Susan Shore** agreed to be on the podcast, but that will be later in the year, when she has published her research. She is working on a new treatment for tinnitus, based on bimodal neuromodulation.
- And **Thanos Tzounopoulos** agreed to be on. He received a 2-million-dollar grant from the **US Department of Defence** to develop a drug for tinnitus.

So, a lot of interesting guests coming up.

Markku: Yeah, and on top of that we got a lot of feedback from listeners with suggestions. For those of you who don't know, we have this dedicated thread on **Tinnitus Talk** where you can submit your ideas for future guests and topics we should discuss. One of them is Meniere's Disease. Then we have natural remedies and scams. As many of you know, tinnitus is rife with scams. There's promises of a cure and effective treatment, but many of those have no scientific basis. And I think it's important we can teach our listeners how to spot pseudoscience and not to waste their money on something that definitely will not work.

We will probably have an episode on sound therapies. And on educating doctors. I think most of us would agree, when we go see a doctor they might not be all that clued up on tinnitus and their attitude might be lacking. So if we can create an episode on what patients expect from their doctors, and we can then share that with doctors and professionals. That's something tangible we can do for the benefit of the patient.

And we will follow up on all the ideas and suggestions and hope you keep sending them in. Besides that, we also want to try new formats, like panel discussions and shorter segments. We might have listeners call in live and interact with us, maybe ask questions to researchers or whoever we have on the episode. I look forward to all of that. This is our fifth episode, and at the end of this year I hope we are maybe at ten or so, and you have been with us all this time.

So, Hazel, can you tell us more about your experiences at the TRI conference? TRI stands for Tinnitus Research Initiative. Their annual conference was held this year in May in Taipei. Hazel was there for a full week. So, please tell us a little bit about that.

Hazel: I was very lucky to be there. I was one of the very few patient representatives there and I think it's so important that patients are present at these events and report back to the community about it. We were very lucky to get some funding from Frontiers, the academic

magazine publisher, to be there. It was very hectic for me, because I wanted to listen to the talks, and interview people, and network, it was really too much. I wrote a blog post with my assessment of the conference, some positive and negative critique. You can find it on **tinnitushub.com** under "Blog".

But I'm most excited about all the video interviews I conducted, with over a dozen, I think even 18 or so, individual researchers. With some big names as well, we got **Susan Shore** talking about her new treatment, **Dirk de Ridder** talking about brain stimulation, **Josef Rauschecker**, lots of names. So that's something hopefully for everyone to look forward to and get a taste of the conference.

And I'm very excited about next year, because it will be in Vancouver, and it will be much easier to go with more people, because we have members based there who can hopefully be part of our volunteer team, so we can cover it much more extensively.

Markku: Cool, that sounds so awesome. Hazel, I personally and on behalf of the tinnitus community, want to thank you that you keep doing this for all of us. The fact that you travelled to Taipei by yourself, you handled most of it yourself, except for the video guy we hired, but it was an amazing effort. What you have done in the past year for the tinnitus community, is something I'm proud of and I look forward to continuing working together in future. We make a great team.

Hazel: We do! Thank you so much.

Markku: Before we wrap up, I would like to remind everyone that you can become a **Patreon** supporter of the Tinnitus Talk podcast, and it won't cost you a lot, it's as little as the price of a cup of coffee per month. And besides ourselves – I, Hazel and Jack Straw – supporting the podcast financially, we now have 8 other supporters, for which we're very thankful. But to make this even better and to be able to maybe travel to meet guests and get better equipment, we would really appreciate your support. You can find more information on this on our podcast website at **tinnitus.com/podcast**. Just look for the 'donate' button at the top of the site.

I would like to thank everyone for tuning into this episode. I would like to thank Steve and David Stockdale and of course Marcelo Rivolta for taking time out of his busy schedule to record this episode. I look forward to meeting you in one of the next episodes, and bye.

Hazel: Thanks everyone, catch you next time!