00:00 Is Tinnitus Like Pain?

Hazel: Hello, and welcome to the Tinnitus Talk Podcast. I'm your host, Hazel, and I'm here today with Peter McNaughton, and we're going to discuss, I think, a very intriguing topic, which is the connection between tinnitus and chronic pain. Because Peter originally is a pain researcher, and I think it'll be very interesting to hear from him how he got from there to being interested in researching tinnitus.

And I think we can all learn a lot about the connection between the two. So welcome, Peter. Thank you for being here today.

Peter: It's a pleasure.

Hazel: So, if you don't mind, could you start just telling us a little bit about your general academic background and research interests and then from there take us through your pain research and how that ultimately led to you developing this interest in tinnitus? Because it doesn't happen so frequently that researchers from other fields think: "oh tinnitus, that's an interesting area to research." So if you could just take us through the journey of how you got here, so to speak.

Peter: How I got here. Yes, I began in physics.

I was a New Zealander by origin, and I started working in physics, but as time went through in my undergraduate degree, I decided I wanted something a little closer to home, so I decided to ... People told me the brain was the new frontier, and I thought, yes, of course, that's right. But the brain really seemed rather too difficult to tackle, so it seemed to me a good nervous system to understand was our sensory systems: vision, hearing, touch, and pain. And I've worked in a number of these areas over the years.

Now, for the last 20 or so years, I've worked in the field of pain. In the mid-90s, the molecular basis of vision began to be understood pretty well, and I decided that it was time to move on and do something else. And the pain field was really a rather primitive field in those days. Experiments were carried out, rather gruesome experiments in retrospect, by people who strapped cats to tables and applied various stimuli and things, but it seemed to me that bringing the new frontier of molecular and cellular biology into the pain world was the right thing to do, and was something that would get it ahead quite quickly. This was a very good idea. The only problem was it was an idea that a lot of other people had at the same time, so there was a sort of influx of molecular biologists and cellular biologists into the pain area. I'm very happy to say that the pain field has advanced enormously in the years since I entered it, not entirely due to my own efforts, but I think I've made my contribution.

And it did seem to me that tinnitus was rather like pain. For a long time, pain was thought to be pretty obviously something that began in the peripheral nervous system. Drop a brick on your toe, there's not much doubt about what's initiated the pain. But in the pain world, what's clinically matter of most concern is chronic pain. That's the sort of pain that needs to be treated. And chronic pain, of course, is very dissociated from any original injury, or maybe there is no actual visible injury. So the concept began that pain somehow, although it was initiated in the periphery, that it migrated into the central nervous system and became something called central sensitization.

Now, it seems to me that tinnitus, and I'm really a bit of an outsider in this view, I have to say, in the hearing field, it seemed to me that tinnitus was rather similar. There's no doubt that tinnitus is initiated in most cases by a peripheral event, going to a rock concert or something like that. Or else sometimes there's a schwannoma, a tumor, which presses on the auditory nerve.

It's initiated peripherally, but most people in the field believe that then it somehow migrates into the central nervous system, and that it's a central nervous system phenomenon. So I could see parallels with the world of pain there, and I just began to ask, why does it have to go into the central nervous system?

What evidence is there for that? And when you look into it, as so often happens with these assumptions that dominate a whole field, when you look into it, the evidence that it is a central nervous system event is pretty thin. it's true that nerve activity changes in auditory centres in the central nervous system in response to tinnitus.

But where does it start? What's its origin? And it seemed to me that it was entirely plausible that it could have a peripheral origin.

Hazel: And listeners might not necessarily understand that is indeed, as you hinted at, a little bit of a controversial view. Certainly, when it comes to tinnitus, I'm less familiar with the status quo of research on chronic pain, but certainly when it comes to tinnitus, when I talk to tinnitus researchers, most of them will make this claim that, yes, the original cause, trigger, whatever you want to call it, is in the periphery.

So it's typically it's hearing loss or it could be some kind of other kind of injury to the ear. It could be head or neck trauma. There's a list of different causes that somehow trigger the tinnitus signal to start along the auditory pathway, but from there it becomes more of a top-down phenomenon in a way where your brain just keeps this going, even if you would completely cure the hearing loss or whatever else the original injury might have been.

So I think that's the theory that's more common, wouldn't you agree?

Peter: Oh, I'm in a minority of n =1 in this view that it's peripheral. But, sometimes it takes an outsider to come in and have some novel and radical ideas, maybe shake a field up a bit, I would hope to do that, although, I've really only been working in the auditory field and the tinnitus field for about three or four years now.

So I'm definitely a Johnny come lately, and I could be wrong. I've been wrong before, and I anticipate being wrong again many times in my life. In fact, I look forward to it.

Hazel: I think it's a healthy attitude in science, for sure. And I want to ask you more about what model of tinnitus you're envisaging, but before I go there, do you have any personal connection to this topic?

Because I'm still curious as to ... you say it just got on your radar because you saw comparisons with chronic pain, but still it doesn't seem that obvious of a topic to just pick up since there is so little

research on tinnitus, comparatively speaking. So do you have any personal connection to the topic or is there some other reason that you picked this up?

Peter: No, I don't have any personal connection. I just thought it was scientifically interesting. And, it's not just a matter of my curiosity being piqued. Of course, a better understanding of what actually drives pain or tinnitus or whatever can lead to the identification of molecular targets that a particular drug might bind to.

So a full understanding of a pathology, this is true also for cancer, heart disease, et cetera, a full understanding of a pathology leads to the opening of routes to treat that pathology. So in my mind, basic science leads and medical science follows. And some medics may disagree, but hey, it's my view.

08:48 Mechanisms of Chronic Pain & Tinnitus

Hazel: So on that note, how would you describe for the layperson your theory of the underlying mechanisms of, let's start with chronic pain, maybe first, and then how you think this could relate to or have some similarities with the underlying mechanisms of tinnitus?

Peter: In the case of pain, once again, I sometimes say to my students, you can do an experiment tonight.

All you need is the privacy of your own room and a brick. Drop a brick on your toe and you will understand all about pain. The next day, your toe will be swollen and throbbing. And that is chronic pain, chronic inflammatory pain. There's no doubt, as I mentioned before, that pain is initiated in the periphery.

And how does it get to the central nervous system? Obviously, it travels up nerve fibres. And it travels up nerve fibres in the shape of very brief little pulses of electricity, which are called action potentials. And typically as I'm sitting here, I feel no pain whatsoever. And my pain nerves-- and there are specific nerves which are responsible for detecting pain.

Of course, we have other ones that detect touch, or the position of a limb, or heat, or coolness, or whatever, the non-noxious sensations. But we also have specialized pain fibres that detect only pain. And as I said, as I sit here, I have no activity whatsoever in any of the hundreds of thousands of the pain fibres in my body, because I feel no pain whatsoever.

And I think in that respect, it's probably an analogy to tinnitus, because it's now known that there are different classes of auditory fibres. There are ones that have a very low threshold, and which are used for detecting quiet sounds. And then there's an intermediate range, which detects louder sounds.

And then right at the top, you have the 'pain' auditory fibres, which detect very loud sounds. And it would be, my view, unproven, but if you're looking for an analogy with the world of pain, it would be those fibres, which are probably the originators of tinnitus. So those are fibres which, like the pain fibres in your body, remain completely silent until a very loud noise triggers their function.

So I think there are analogies also with pain. When you talk about ...

Hazel: Sorry to interrupt, when you talk about those fibres, can you be a bit more specific about where those are? Are we talking about the auditory nerve fibres or are you talking about the cochlea?

Peter: We're talking about the auditory nerve fibres.

So the way the auditory nerve system is set up, and this is a very simplistic description, but we have the hair cells which actually detect the sounds coming in, but those are just tiny cells that don't have any fibre or axon which comes out of them. And they immediately form a synapse, a connection with a second type of nerve cell, which is called the spiral ganglion, or SG nerve cell. So these spiral ganglion nerve cells are like the second order cells in the pathway, and they follow the cochlea around, which is why they're called spiral ganglion, because they're arranged in a spiral, as indeed are the hair cells as well.

So the hair cells transmit their signal of the sound onto these spiral ganglion cells. And just like the pain cells, these spiral ganglion cells have long axons, which enter the central nervous system and make a synapse in the first central way station on the auditory system, which is called the cochlear nucleus.

So that's rather like the way stations for pain. This way station is within the upper reaches of the spinal cord, but still within the spinal cord. Okay. And from there onwards, the signal goes through a number of different way stations until it reaches the cortex. The analogy with the touch and pain system is not only a functional analogy, it's also an anatomical analogy.

Hazel: Let's take the typical cause of tinnitus, which is hearing loss, could you describe how we go from diminished hearing to then consciously hearing a tinnitus signal?

Peter: I think there's probably an analogy with an extremely unpleasant pain condition which is called neuropathic pain. And this can be precipitated by a very wide variety of different syndromes.

Injury can do it. Sometimes the injury heals without pain, sometimes it doesn't. Or a number of other conditions are thought to be possible, like fibromyalgia or diabetic neuropathy-- horrible conditions that last for many years. And people used to think these were central nervous system problems, so they were very much like the view about tinnitus.

But there's a growing understanding that actually pain fibres, pain nerves, that are supposed to be, if you have no pain, completely silent. All hundred thousand or a million of them present in my body, every one of them is silent, and I feel no pain. But repetitive activity is set up in those nerves, which precipitates this so called neuropathic pain. Neuropathic because it's a pathology, neuro because it's in the peripheral nervous system. The understanding of neuropathic pain has migrated outwards. Instead of the pain migrating inwards, our understanding is migrating out from the brain.

Believing, and it's something that I think there's a lot of evidence for, believing that neuropathic pain is of peripheral origin. Now that's not to say that it's not modulated by central events. So people who suffer from neuropathic pain may be very worried, I would be worried. And that may make their perception of their neuropathic pain worse.

I'm not saying that it's not subject to a lot of central modulation, just as our auditory stimuli coming in. The origin of neuropathic pain is now thought to be in the periphery. And from a practical point of view, things that are in the periphery are much easier to treat because we're talking here about drugs which are going to interfere with the function of your nervous system in order to suppress tinnitus or neuropathic pain.

And drugs that can interfere with your nervous system obviously have the possibility, at least, of interfering with consciousness as well. But there's a blood brain barrier which exists between the periphery and the central nervous system, and the same blood brain barrier also intervenes between

the auditory system, which is in the periphery, and the first way station, the cochlear nucleus, which is in the central nervous system.

16:52 Ion Channels

Peter: So if you want to treat pain or neuropathic pain or tinnitus, what you want is a drug which is peripherally restricted, which doesn't enter the central nervous system. So just by having a phenomenon which is present in the peripheral nervous system, and a drug which is restricted to the peripheral nervous system, you overcome some of the worst problems of the efforts to date of treating, for example, tinnitus, which is that the drugs used to treat the tinnitus-- and actually there aren't any that are very successful, but some of them give some small effects-- the drugs that are used to treat tinnitus are liable to have effects on consciousness or on mood and other central nervous system phenomena.

Hazel: And if your theory is right, that it is a peripheral phenomenon, we could avoid all of those potential problems with drugs influencing the brain, which can have all kinds of unwanted side effects, right? But the treatment could actually be a lot simpler, that's what you're saying.

Peter: Correct, correct. We may be on the wrong track, I'd be the first to admit it, but we can but dream. So there is this wonderful future where a peripherally restricted drug could abolish tinnitus with no psychotropic effects at all.

Hazel: So let's go into ion channels because I know the treatment that you're working on centres around that and a lot of people won't know what an ion channel is. So if you could describe that and then explain how you hypothesize those to be related to both pain and tinnitus.

Peter: Okay, I can recapitulate how puzzled I was when I first became a neuroscientist.

I learned about ion channels, and are they spelt I R O N or are they I O N channels? And I soon worked out that they are I O N channels. So they pass ions. So a common ion that's passed by an ion channel, which is like a little hole in the surface membrane of the nerve fibre, a common ion is sodium.

Now, sodium is positively charged. There's a lot of it outside and there's very little inside the nerve fibre. So these ions are not only selective little holes that, for instance, let only sodium through, or potassium, different ions have different channels, but they're also capable of being opened and closed.

If an ion channel is opened, that means that sodium ions can come in. They will 'want' to come in, because there's a lot of them outside and very little of it inside. The positive charge carried by the sodium ions, if the channel's open, the sodium ion comes belting through, which makes the inside of the tube, which is the axon, positive.

And that's the stimulus for setting up activity in the nerve fibre. So instead of lying completely quiet, as your pain fibres should be, and as mine definitely are, all of a sudden there will be activity. So if I was to squeeze my toe with some pliers this would set up influxes of sodium ions that would make the interior of the nerve fibre more positive, and that triggers off what we call an action potential, which goes zipping up towards my brain and gives the specific response: "Ouch, stop pinching my toe with your damn pliers, please."

Hazel: So that's how pain signals are transmitted. And then you talk a lot about HCN2 channels. I also had to look up what that meant, but again, could you try to describe for lay people what HCN2 channels are?

Peter: Okay. The nervous system of course, is extremely complicated. We, our brains, are, they say rather grandiosely, the most powerful and complicated things in the universe, but we've never met any aliens so far, so they may do better than us. But still, certainly our brain is extremely complicated, and it's capable of doing many different things. So a lot of different ion channels are required to make it work.

So there are hundreds of different ion channels. But the ones that we're interested in, I've already explained about them, these HCN2 channels, they're like little pores in the external membrane of a nerve fibre. And if they're activated, and they are activated by painful stimuli, then they will allow electric current carried by sodium, positively charged sodium ions, to enter the nerve axon, which makes the internal voltage more positive, which in turn, and this has been a very well-studied phenomenon, makes the nerve axon fire repetitive action potentials.

So if you recorded from a single nerve fibre and applied a squeeze to a toe or something like that, you would get these action potentials which signal pain, and it's been known for many years that there's not a very complicated Morse code here.

Basically, the faster the axon is firing, the more intense the sensation will be. That could be pain, or it could be touch, or it could be light, it's true for all sensory systems.

Hazel: So how did these HCN2 channels come on your radar as a potential therapeutic target?

Peter: They're channels that are normally quiescent. So they're just lying there waiting to be activated by a pain stimulus. So my HCN2 channels, like my nerve fibres, are quiescent. They're just lying there waiting to be activated by a painful stimulus of some sort or another. The fact that they fulfill this function does make them attractive targets for blockers which can prevent them from opening and therefore prevent pain. But the problem has always been we want to have normal sensation, normal touch, and normal pain as well.

There's no point in abolishing the sense of your finger being trapped in a door. That's what we call acute pain, and it's clearly different from normal sensation, and it warns you not to get your finger trapped in that door again. So acute pain is a very important sensation in terms of the preservation of our bodily integrity or even our lives.

So the trick has always been to abolish chronic pain, or neuropathic pain, which is a sort of subset of chronic pain, to abolish chronic pain without affecting acute pain. And this was the remarkable thing that we discovered, that blockers of these HCN2 channels can do, they can block chronic pain, diabetic neuropathy, migraines, they work very well against migraines, etcetera, but they don't affect normal pain sensation.

And what I hope is that some of these drugs that we've developed, when I say developed, they haven't been developed to the stage when they can go into people yet, but we've got some quite nice drugs that do the right things in animal models of tinnitus and also of pain. These drugs block only chronic pain.

25:14 Could HCN2 Inhibitor Drugs Work on Tinnitus?

Peter: And what we hope is that they will block tinnitus without interfering with normal auditory sensation. Because I think any person who suffers from tinnitus, they would not accept to have their auditory sensation interfered with. You might as well cut their ears off if you're going to block their normal auditory sensation.

So it has to be selective enough to block tinnitus, but not too much affect normal auditory sensation.

Hazel: So the drug or drugs-- we can get into that in a moment-- that you're working on, they are blocking HCN2 inhibitors and so they could potentially inhibit chronic pain. How did you find out, or was it just a theory that you had, how did you find out they could potentially also work on tinnitus?

Peter: This really began with a visit to our department by Alan Palmer from the University of Nottingham. And Alan gave this lovely talk on tinnitus, which I knew very little about before.

And he also described a very clever way of measuring tinnitus in animals, such as mice or guinea pigs. And it seemed to me that we could do some quite simple experiments. They have these guinea pigs in which they've been exposed to a loud sound while they were unconscious. They were anesthetized, exposed to a loud sound, and then you could find, later on when they've recovered, whether they've got tinnitus or not.

And I suggested to Alan that we could try some of our drugs on these guinea pigs that they were using and see whether the drugs alleviated their tinnitus. So this was a complete shot in the dark, but it actually gave very promising results really quite early on. So that was really how things started.

So I proposed to Alan that we might make a project out of this and work together with some of my drugs and some of our ideas and try out to see whether the idea has legs. And I have to say the work that we've done since has really been very promising in terms of its advances. It's not been published yet, I have to say, because we're still working on this, but we're getting pretty close to publication and things look good.

Hazel: It's really interesting that you thought, let's just take that shot in the dark and see if this works.

Peter: Hey, nothing ventured, nothing gained. I have to give a lot of credit to Alan Palmer and his collaborators who firstly, they had the expertise in auditory systems and how to measure tinnitus and things like that.

The only thing that I brought to the collaboration was a novel idea, and all credit to them that they were prepared to give me the time of day, I think, because the ideas that I've been talking to you about, and the ideas that they were accustomed to, really run very counter to one another, particularly in this idea that tinnitus is a peripheral rather than a central phenomenon.

But our drugs are peripherally restricted. They do not get into the central nervous system, and they provide very good relief of tinnitus in animal models.

28:44 Relation to Similar Research Projects

Hazel: So we'll get a little bit more into your drug discovery process in a moment, but one final question on ion channels. There has been other work from other researchers on the connection between tinnitus and different channels, most specifically Thanos Tzounopoulos has done a lot of work on KV7 channel modulators.

And I think there's also a paper from Arnaud Noreña on KCC2, which I'm actually not sure if that's also an ION channel or not. I thought it was something else, but I couldn't figure out what it was. But could you maybe just briefly say something about other work that you are aware of that's in a similar vein and how your work relates to that.

Peter: Okay, both of these groups are using the hypothesis that their drugs act in the central nervous system. And specifically, they've looked at the cochlear nucleus, which is the first way station when the auditory fibres enter the central nervous system.

So the Tzounopoulos idea is, in essence, a rather simple one. I've talked about how if you open sodium channels, that tends to cause action potentials, electrical activity to arise in nerves. But their idea is in a sense the reverse. Because potassium concentrations are high inside the nerve and low outside.

So if you can open up a potassium channel, potassium ions leave the cell. They will 'want' to go out because the concentration gradient is driving them, which makes the interior of the nerve cell more negative. So that tends to oppose the generation of action potentials. While HCN2 channels, which are essentially sodium channels, will tend to promote activity in the nerve fibres.

So it's very rational to try potassium channel openers to damp down repetitive nerve activity that's causing tinnitus. Whether that's in the periphery or in the central nervous system, it doesn't much matter. But if you could damp down potassium activity by opening potassium channels it's likely to oppose tinnitus.

And the drug that they're interested in is actually derived from a well-known anti-epileptic drug, which is called retigabine. And so retigabine's been used clinically for epilepsy for some time, and precisely for the reason that epilepsy is repetitive activity in the central nervous system that causes a fit, obviously.

And you could oppose that, and indeed if you record from nerves during an epileptic fit you will find they're going crazy, brrrrrr, when they're supposed to be just going pip, that sort of thing. So retigabine is a successful anti-epileptic, simply because it damps down the excitability of those nerve fibres.

When I say successful, it's not terribly successful. It's little used nowadays because it has significant side effects. And I think you can see why. If you're dampening down activity in all of your nerve fibres, then it's going to have sedative effects as well as anti-epileptic effects. If you're an epileptic, you're desperate,

you'll want to take anything that will help you. So the retigabine has a number of other unpleasant effects, makes your skin turn blue and things like that. So they have developed a derivative, which is a chemical modification of retigabine, which appears to have some effect in animal models at least.

Don't think it's been tried in humans. So it's a not totally different idea, but it's certainly with a different target, which is potassium channels, opening potassium channels instead of closing sodium channels, which are our HCN2 channels. The other paper, Arnaud Noreña, this again is a different hypothesis and this is really based around chloride gradients.

So chloride in nerve cells is more concentrated on the outside than the inside. So if you open a channel that's permeable to chloride ions, you're going to tend to dampen down the repetitive activity in the nervous system. So effectively, they're trying to do the same thing but by a different route.

So their idea is a transporter of chloride which kicks chloride ions constantly out of the axon so as to maintain that chloride gradient. And if you, just let me get this right, once again they're focusing on the cochlear nucleus, and they're trying to, I think, enhance the activity of the chloride transporter so that it produces more inhibition and dampens down the nervous system.

So they are, in a sense, tackling the same problem but in different ways, but the difference between their views and what we've got is that they are focusing on the central nervous system as the proposed

target. In fact, the cochlear nucleus, which is the first way station. So what they're saying is that tinnitus develops in the cochlear nucleus.

That's the target. What I would say is that tinnitus is initiated peripherally in the spiral ganglion neurons and is transmitted into the cochlear nucleus. The result for the cochlear nucleus is the same. You'll record enhanced activity in the cochlear nucleus caused by tinnitus, but the origin is different.

35:05 Drug Discovery Process

Hazel: That's very clear. Thanks. So let's talk a bit more about your drug discovery process. What have you done so far in terms of testing HCN2 inhibitors? I understand you've conducted various animal tests also for different conditions. Can you talk a bit more about that? And then, which phase actually are you at now?

Peter: Okay, drug discovery, as I discovered myself, is extremely hard. And you've got to set some criteria at the start and say our drugs are going to do this and this. Drugs for neuropathic pain obviously have to work for neuropathic pain. They have to do what they say. But there are a lot of other criteria that you have to meet.

And one of the big problems is selectivity. So we're very unfortunate in that respect, in that HCN2 channels drive pain, and we also believe tinnitus. But there are closely related channels, or cousins, called HCN4 channels. They're structurally very similar, and unfortunately drive the heart rate. Now, the heart rate is something you cannot afford to interfere with because if the blocker works magnificently on HCN2 channels, but also blocks HCN4 channels, then you'll have trouble walking upstairs.

You won't be able to pick up your grandchildren, etcetera. So there are severe consequences. And of course, this is obvious and everybody's aware of this. Apart from the fact that the drug has to work, it also has to be selective for HCN2 channels over HCN4 channels. And that's a very hard ask, because these channels are very similar to one another.

They're not identical, and we have succeeded in making some selective drugs. But it wasn't easy at all. And then, on top of that, you've got another whole list of things that have got to be met. As I said, drug discovery is very demanding. People won't tolerate taking drugs every hour. So your drug has got to last a long time within the body so that people would have to take it only twice a day or maximum three times a day.

People won't tolerate more than that. So we've had to overcome all of those problems. This is a question of drug lifetime. How rapidly is the drug metabolized? Then there's another problem. It's a scary thing, which I knew very little about before we started this, but people don't like injecting drugs.

They want them to be, as we call it, orally available, a pill that you can pop in your mouth. And unfortunately, that's another very hard ask, because in order to cross your intestine, enter the bloodstream, and not get completely metabolized by the liver, it is really quite a difficult thing to do. So we've made some pretty selective drugs that are selective for HCN2, the one we want to hit, over HCN4, which drives the heart rate. We've got some quite selective drugs and they work very well in animal models of pain and also in tinnitus, but they don't have enough lifetime and they're metabolically unstable. In other words, they're broken down too quickly in the body and they don't have good oral availability either.

So we've got a lot of work to do to overcome those problems, but at least the principle works very well.

Hazel: Yeah, so you run into all these obstacles, you think you've solved the selectivity issue so as not to inadvertently tamper with people's heart rate, which obviously one would like to avoid, but you're left with this other major problem, which is the lifetime of the drug. So how do you propose to crack that problem?

Peter: People in the pharma industry have enormously much more experience of these things than I do myself. What we need to do is to work with pharma companies in order to try to crack these problems. Now, the simple way to go about it is just to make lots of different drugs.

You start with a particular chemical framework and put a nitrogen here and take out an oxygen there and things. And it's essentially empirical. You just tinker with them, each time testing them to see if they've got good selectivity, good lifetime, etc. And the hope is that, one day, bingo, you'll get a nice drug, which belongs to a family that you started with. So you've tinkered with this structure of an existing ...

Hazel: So do you essentially have a family of promising compounds? Is that the way to look at that? They're all mostly similar but slightly different?

Peter: Yeah, we do. We have a very large family of about 500 such compounds.

And there were three main scaffolds that we started from. And we made a lot of compounds from those scaffolds. My feeling at this stage is that we need to do what they call scaffold hopping, which is hop to a new type of scaffold. And how do we do that? The advance of artificial intelligence may help us there.

There are actually now computational ways of looking at drugs, they're not real drugs, they're just structures of drugs, and asking: is that going to bind nicely to our target and avoid binding to the HCN4 channels that drive the heart rate, for instance. So this is a very recent field that's exploded really just over the last two to three years.

And I think there's a real possibility that artificial intelligence can help us. Before we get into that, which would be a long road and a lot of money, a very large amount of money, I do wonder whether some of our existing drugs could have their lifetime improved. And there are some quite simple things that you can do to do that.

One is just a slow release formulation. So you package your drugs in little vesicles, which firstly helps them navigate across the intestine and into the bloodstream, and secondly slows down the rate at which the drug is released. So your drug may not have a brilliant lifetime, but with what they call formulation, a slow release formulation, you may be able to get something that's clinically useful.

I think in terms of what we'd like to do, that would be our first step, and it would only be if that failed that we would go on to the much more sophisticated step of trying to hop to a new scaffold and trying to develop drugs that are really different from the ones we've got already. And it would be very expensive to do that.

Hazel: You mentioned expensive. In order to do any of this right now, you would need a significant amount of funding, which it sounds like most likely would come from a pharma company. Do you have any prospects in that regard?

Peter: Yes, we do. We worked with a very big and very good pharma company, Merck, for about five years. They produced a huge number of novel compounds, but they weren't in the end satisfied that they were of sufficient lifetime and sufficient selectivity to meet their criteria. So regrettably they gave

up the effort. I do understand, there's only so much money you can spend and they spent an awful lot of money doing this.

So right at the moment, we're looking for more funding or collaborations with further companies to take a different view on the matter and try to get forward. I have to say this sort of trajectory is rather common in drug discovery, and most drug discovery efforts fail. I'm not really prepared to give up on this one yet.

So I'm working on the hypothesis, firstly, that some of our existing drugs may be good enough to go into the clinic with improved lifetime. But after that, there is a much more expensive process, but it's not completely novel, so we could take the information that we've already got from our existing compounds and think maybe we can hop to a new scaffold, which has got, for instance, a longer lifetime. So it looks a bit the same, but it perhaps doesn't have the metabolic properties that are rather disappointing in our existing drugs. But I'm not prepared to give up yet.

Hazel: No, nor should you. And I think tinnitus sufferers will commend you for sticking to it.

44:51 Getting Pharma Companies to Invest

Hazel: But let's say you get the funding for the next steps and you find what seems to be the perfect compound, and it's very promising in the animal studies. Then the next step would be human clinical trials. Now, a recurring issue with potential drugs for tinnitus, or maybe for any condition, I don't really know, but that step from animals to humans, that's also often where drugs fail, right?

The translation from animal to human models doesn't always work. It's hypothesized for tinnitus that this might be because humans have much more complex higher brain functions, which are thought to be involved in tinnitus. Although according to your model, that maybe shouldn't matter so much. But do you think this could be a risk for your drug candidates?

Peter: It's certainly true that in the pain fields, a number of animal models have failed to provide this leap from animals to humans. So things that work perfectly well in animals, for some reason don't work very well in humans. My own view, looking back on a number of these sort of high profile failures, is that often their work had leapt too early into a hypothesis about what causes pain and where it comes from, particularly in the pain field, this was a problem. And I think, with a better understanding now of what pain is and where it comes from, we can think: "Oh yes, it's obvious why these drugs failed, because they were looking at pain the wrong way."

So particularly in the pharma industry, I'm afraid there's a lot of pessimism about animal models of pain and also of tinnitus. But what else can you do? There is nothing else you can do. The only other alternative, if you don't believe in animal models is to go straight into humans. Doing human experiments is hugely expensive and also risk prone as well.

Unfortunately, there have been some high profile disasters in a number of areas in phase one trials where people have been seriously injured or even killed, and so human experiments are not without their problems as well. I think what you've got to do is to make sure that your animal model really does reflect the condition that you want to treat.

In other words, is the animal really mimicking what you want your humans to do? And also to have a proper understanding of what actually causes pain. And I believe the same will be true for tinnitus. One advantage of starting off with tinnitus is that there are no drug competitors out there.

There really isn't anything that works at all well for tinnitus. While for pain, drugs have their side effects, and they don't work very well, but there are drugs out there which provide some relief for a small number of people, at least. If you asked me where I would start with my hypothesis that pain and tinnitus are rather similar to one another, I would say it might be rather good to start with the tinnitus market because pain is clouded with psychological difficulties and people get very depressed about their pain.

If it was me, I would be depressed if I had chronic pain. Tinnitus, I think, is perhaps a little bit more free of psychological problems associated with it. People know they've got tinnitus, and if they take something that gets rid of their tinnitus, they're going to say, "wow, it's gone!" Even if only for an hour or two. And then you can improve on working up the drug lifetime, because you know you're on the right track.

Hazel: I agree with you, but I think there's a lot of researchers that are very much psychologizing tinnitus, right? And, a lot of the treatments that have been developed are essentially psychological treatments that help you cope or habituate to the sound. and so in that sense, it's been psychologized.

But you can still maybe more clearly than with pain make a distinction between the tinnitus signal and your reaction to it. And those are two different things, right? But what we want in the end is to get rid of the signal, because we know, unfortunately, that there are a lot of people out there that can't just learn to live with it or who do find it extremely bothersome. So I'm glad to hear that you think tinnitus should be prioritized because there are already existing treatments, however imperfect, for pain. I would say, though, that the healthcare industry doesn't necessarily agree because I don't see them jumping on the opportunity to develop treatments. Tinnitus treatments. In fact, I see them more or less shying away from it. Have you observed the same or is there reason for optimism?

Peter: Tinnitus may be unpleasant, it is unpleasant, but it's not as bad as neuropathic pain. To be in constant pain, people that are in constant pain from diabetic neuropathy or something like that, they can't concentrate, they can't think, their lives are blighted by this horrible pain.

I think without minimizing the importance of tinnitus, I think it's in a lower category. I think it was Julius Caesar who said that his men are prepared to face death, but they will not face constant pain. But the disadvantage of testing a new drug in the pain field is that most people with terrible chronic pain are on something already, and it will be something that doesn't work very well and that causes unacceptable sedation, etcetera.

But they'll be on something, which makes it a bit of a problem to work out if your drug is doing anything over and above what the existing drug is doing. The tinnitus market is generally felt by big pharma to be smaller, the number of people that are suffering from tinnitus. And the amount of money they're prepared to pay to get rid of it is less than it is for pain.

And we live in a capitalist society and the drug companies are driven by making profits. So drug companies may be more interested, or they are more interested, in pain than they are in tinnitus because the profits there potentially are greater. I'm sorry to be blunt about this, but this is really the way the drug world works.

So the reason that I say that tinnitus might be a good place to start, if we believe that they are similar syndromes, something that starts in tinnitus could relatively quickly leap over into the pain field, the much larger pain field. Migraine, for instance, absolutely huge field. Cures for migraine, there is no

cure for migraine, but some better treatments that have come along in the past few years have been hugely welcomed.

But the advantage of working on tinnitus is firstly people have no treatment, so there's no background there to compare it against. And secondly, it's rather free as well of psychosomatic consequences. So this is just an idea, but it might be a great test bed start, and then if a drug works in the tinnitus field, the same drug or a similar drug could perhaps move out sideways into other fields like pain, migraine, etc.

But this is just a hypothesis.

Hazel: But it sounds like that could be a good business case for pharma companies to want to pick it up because if it was just about tinnitus, maybe they wouldn't be so keen, right?

Peter: No. Tinnitus is a significant market. I'm not saying it's small. But it is a lot smaller than, for instance, the migraine market.

Hazel: No, the commercial interest is just less, right? But if you can make a business case and say: "Look, if this works in tinnitus, probably we can expand into these other fields." Suddenly, it's probably a much more commercially interesting proposition, I would imagine.

Peter: It is. And that would be the idea. Yes. Something that works in tinnitus could move sideways later on.

53:59 How Quickly Can Peter's Drug Come to Market?

Hazel: I see, yeah. in your best case scenario, if everything goes smoothly, when could human clinical trials happen?

Peter: It's very difficult to predict. If this formulation approach that I mentioned before was successful, then yes, we could think about moving into the clinic in three, four, five years or something like that.

If we have to initiate a new drug discovery campaign, then it's likely to be considerably further down the line. So to develop our present suite of drugs of these 500 compounds that we tested, this took us about five years. So with a new chemical starting point discovered perhaps by AI or by a sort of more manual process called scaffold hopping, we could start again and develop new drugs, but we would be talking about five to seven years if things worked.

Hazel: Yeah, I think it's important to be realistic about these things because people get their hopes up when they hear about potential new treatments, but I also feel a responsibility to educate them about this. This is not just around the corner, unfortunately. One of our listeners also asked the question that if you do get to human clinical trials, would the new trial guidance in the UK help to get it to market quicker? I'm actually not familiar with the new clinical trial guidance, but maybe you are.

Peter: Yes, the clinical trial guidance really says that if a clinical trial that's underway is showing signs of success in some horrible disease like cancer or heart disease or something, then it could be sped up and got into to clinical practice, widespread clinical practice, more quickly.

Because of course, it may seem bureaucratic obfuscation, but the number of hurdles that a drug's got to leap before it actually gets into general practice are very numerous and very large. And this, I'm afraid, is because there've been some high profile failures that have caused horrible things in the past.

Behind every bureaucratic obfuscation there lies people that have died, basically. Attempting to speed things up, I think, is a good thing, particularly when there's a good chance that the drug is not going to have side effects. And we saw an example of that during COVID, when these brand new messenger RNA drugs came in, in the space of a few months.

This could never have happened in normal medical practice, but because COVID was an emergency, people were prepared to speed them up. And in fact, they work brilliantly well. They would never have been discovered so quickly if we hadn't had COVID. So yes, in some cases, speeding things up can be really brilliant.

But I think it's probably a bit much to think that one could do that for tinnitus, I'm afraid. It's not a life threatening disease. I think it's only in cases of life threatening disease like COVID or cancer or whatever that you could have this sort of acceleration in getting things into the market.

Hazel: Again, it's good to manage people's expectations then in that regard. Peter, we've actually gone through all the topics that I wanted to cover, but I wanted to give you a chance to add anything else that you may want to add or you want our listeners to know about.

Peter: Maybe just a philosophical thought.

I've had a wonderful life in science, it's been great thinking about new ideas and it's even greater when you think of a new idea and it actually works out. Perhaps I could say what is my wish to do with the rest of the scientific life that's left to me? I think I'd like to get some of the drugs that we've been talking about, or one of them, into clinical practice.

I think really to take something from an idea in basic science-- I know I've explained these ideas in rather simplistic terms, but it's not really very much more complicated than that-- to take these ideas right from the laboratory bench into clinical practice and actually to give people relief from tinnitus would be absolutely wonderful for me.

That would be my dream, would be my absolute dream.

Hazel: That would be absolutely wonderful. And I know so many people would be so grateful to you. And by the way, even if you don't succeed, I'm sure people are grateful for to you for trying. But yeah, I know it's not a life threatening condition per se. And I know a lot of people live with it quite comfortably.

But there is unfortunately also a subset of people that do suffer extraordinarily from it and just giving them that relief indeed would be wonderful. So thank you for trying.

Peter: Thank you for talking to me. It's been great to describe what we're doing, and I hope that people are enthused by what I've talked about today.

Hazel: Thank you, Peter.