Hearing Health Hour: The Present and Future of Inner Ear Hair Cell Regeneration
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Lead Presenters: Lisa Goodrich, Ph.D., and Ronna Hertzano, M.D., Ph.D.

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>> ANIL LALWANI: Hello and welcome to our Hearing Health Hour webinar. Today's topic is a hot one, inner ear hair cell regeneration.

These hair cells, in contrast to those on top of your head, are much more important as they make one of the most important senses—hearing—possible.

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By way of introduction my name is Dr. Anil Lalwani, professor and vice chair for research in the department of otolaryngology-head and neck surgery. You can practice that with me: “oto-lar-yn-go-log-y”-head and neck surgery as well as associate dean for student research at Columbia University Vagelos College of Surgeons in New York.

I'm also a board member at Hearing Health Foundation. I oversee the Emerging Research Grants program, also affectionately known as ERG. ERG provides critical funds to researchers studying hearing and balance conditions. These grants have made it possible for many leaders in our field to become successful scientists, even our own speaker today, Dr. Hertzano.

Today we will hear from two individuals from Hearing Health Foundation's *other* major research program, the Hearing Restoration Project or HRP.

The HRP is a consortium of amazing scientists working collaboratively to advance cures for hearing loss and tinnitus.

Our presenters today are the HRP consortium's scientific director, the one who leads it all, Dr. Lisa Goodrich of Harvard Medical School. And I want you to know that I have known Dr. Goodrich, since she was so young. Many years ago, she came to our lab and we worked together to dissect cochleas. And, of course, she is an amazing scientist and you will hear all about hearing restoration [from Goodrich] and from one of our other consortium members, Dr. Ronna Hertzano of the University of Maryland School of Medicine.

Dr. Hertzano, as I mentioned earlier, received ERG funding as well from HHF in 2009 and 2010 making an honest broker of saying ERG creates amazing scientists.

Together they will discuss the biology of inner ear hair cell regeneration. HRP's current work and the direction of future research is only possible through the generosity of supporters like you. If you would like to support our work on hearing loss, tinnitus and related conditions, you can do so today at hhf.org/donate.

Now we will move to the more important part, the presentation. The present and future of inner ear hair cell regeneration. And please do hold your questions for Drs. Goodrich and Hertzano until the Q&A session. You're welcome to add them to the chat. Dr. Goodrich.

>> LISA GOODRICH:
Great. Thank you. OK. Are we all good there? So thank you so much, Anil, first of all, for welcoming me into your lab all those years ago when I decided I wanted to learn about the ear and for all the work you do with the Hearing Health Foundation. It's really very much appreciated.

And I'm happy for all of you to be here and hearing what we are trying to do at the Hearing Restoration Project. So I'll just tell you a little bit about myself. I'm a basic scientist. I have been interested for a long time in how you build a nervous system. It's something I was fascinated by as a child. I came into the auditory system through my training and I have to say it's just been a wonderful community of researchers to be a part of because it has interesting problems and we really want to help people to hear better and having a combination of those things is really fulfilling.

I'm also happy to be here with my friend and colleague, Dr. Ronna Hertzano, and she will provide some clinical balance of the things we're doing, basic science, and she does wonderful basic science as well and it speaks to the way this consortium works. We all work together and learn from each other.

Let's start by talking about the sense of hearing. This is something we can all appreciate, how much it brings to our lives. From an animal's point of view, it is absolutely essential as a way of finding your food and avoiding being food. As human beings our sense of hearing brings us so much more. It helps us to communicate with each other across great distances, you know, through the phone we can communicate emotion, we can communicate everything that is happening in our lives when we have been separated so much, for example.

You can also use our hearing just to enjoy the beauty in the world, the natural world, the musical world and amazingly we can do all these things even when there are a lot of sounds in our environment. We can go to a group and be surrounded by our friends, and hopefully we can do this more as the pandemic winds down and we can somehow listen to the conversation in front of us even when there's music playing in the background. We can extract information from that that tells us something about the way the person is standing in front of us.

And so how does this work? How do we actually collect the sounds and turn them into something that has so much meaning for us? It actually all starts with movement of air. Sound travels as wavelengths and that is moving the air. It is a mechanical thing that has to happen first. Our ears are an amazing machine that collects this mechanical energy and turns it into a signal the brain can understand. It starts with the wavelengths of sound traveling to the ear canal and causing vibration of these tiny little bones shown here next to a dime. These tiny little middle ear bones that are moving because of the movement caused by the sound. Those bones sit here and that will cause vibrations that are detected here in the inner ear by the cochlea. The cells that make this actually happen are the one that Anil referred to and those are the hair cells.

Why do we call them hair cells? It is because of these hairs that protrude from their surface. These are basically movement detectors. When the wavelengths of sound move the bones in the ear this transmits into vibrations inside the inner ear that activate these hair cells. These hair cells will be activated by mechanical force and turn into an electrical signal. Here's what they look like inside the ear. You can see that they can't do this all alone. You can see them here as well, surrounded by all these other cells. These other cells, shown in yellow, are the supporting cells.

And supporting cells are really just as important; they really should not be relegated just to supporting status. They are part of this whole wonderful machine that has to vibrate in response to the sounds and cooperate to keep the hair cells active and alive and to transmit those signals that will go to auditory nerve fibers and onto the brain.

When the system works, it works beautifully but there are so many moving parts that, of course, unfortunately, there are many ways the system can stop working. There are many causes of deafness, from genetic mutations that might keep the hair cells, for example, from detecting the sound to begin with. There are also mutations that can affect the supporting cells and there are mutations that can affect many other cells around them. There are also ototoxic drugs that can affect survival of the hair cells and many other reasons why the ear might stop working.

One of the interesting things is that it often converges on the hair cells. Many forms of deafness will have a hair cell pathology associated. When we look at a healthy ear, we see all the hair cells. You can see what happens in a damaged ear either with too much noise or ototoxic drugs you lose these hair cells. This ends up being a pathology that is associated with many forms of hearing loss.

Right now, how do we deal with this? We need to overcome the loss of the hair cells. Traditionally, we have done this with things like hearing aids, which basically increase the ability of any cells remaining there to detect sound. Or we can use cochlear implants which are a really wonderful way of working around the absence of the hair cells by directly stimulating those auditory nerve fibers. I think all of us right now can appreciate how quickly biotechnology is moving. In the 21st century, we have actually have a lot more options for ways to deal with the loss of hair cells. For one thing, we have a much better understanding why the hair cells die to begin with and we are learning ways to prevent that from happening and that would be ideal. Not listening to loud sounds, for example, but also finding ways to prevent the effects of ototoxic drugs.

In addition we've made great strides in gene therapy and we're starting to find ways to replace the genes that are mutated in various forms of congenital deafness. What I want to talk to you about today is another project we're developing through the project. That's hair cell regeneration. This is not a crazy idea because it actually happens. It happens in chickens quite naturally.

This is what a chicken cochlea looks like. They have hair cells, completely analogous to the cells I showed you before from the mammalian ear. And after noise damage, those hair cells are lost. But, remarkably 10 days later, you would never know something happened. It is completely repaired.

It's much like if you get a cut on your skin you have a scar for a little bit, it heals and then it goes away. This can happen. You can rebuild something as complicated as the chicken cochlea. In fact, the same thing happens in zebrafish. It does not happen in the mature

human ear and it does not happen in the mature mouse ear.

However, we, actually, through the work we have done, have found circumstances in which you can see signs of regeneration even in the mammalian ear and that is really encouraging. So, while it doesn't happen regularly, there is some low-level spontaneous regeneration that can happen in the vestibular system. And in addition, you can also see during the very early stages of life that an injury can lead to replacement of the lost cells with new hair cells. It happens in a much lower level than what happens in birds, frogs, and fish but this capacity is mostly lost altogether from the cochlea before the animal can hear. So it might happen in the first week of life in the mouse for example, and then it is gone. Still, this is really encouraging. It tells us the cells have the capacity at some point of regenerating. It tells us all the genes you would need to regenerate are there and that we can – there is the possibility of putting together something as complicated as the mammalian cochlea from the parts that are left.

Let me tell you a little bit about those parts and what is actually happening. It informs a lot of what we are trying to do through the Hearing Restoration Project. This is a diagrammatic view of what's happening inside the cochlea. The hair cells are shown in purple, the supporting cells are shown here in gray. When there is a damaging stimulus, those hair cells die. They are extruded from the surface and they can actually send signals in the form of molecules that are detected by the supporting cells that basically signal that something bad has happened and the supporting cells in a regenerating ear know how to deal with this.They hear the alert and they come to the rescue.

So what do they do?They actually divide and will divide just once. They divide a limited amount of time and they will produce a new hair cell and then they will replace themselves. And through this we now can rebuild the cochlea or the organ of Corti which is where the hair cells are embedded exactly the way it was before. We replace the hair cell and we replace the supporting cell.

In other circumstances the supporting cell might respond to the signal from the dead hair cell by turning into a hair cell itself and that is a known form of useful regeneration. This is what can happen in the chicken cochlea or the fish lateral line but it does not happen in mature mammals.

This is something we would like to understand. What is the difference? Why is it in some species this happens and not in others? And if we can identify the signals and how the cells respond to the signals and figure out what is different about that, maybe we can come up with ways to overcome this block and basically trick the cells into thinking, for

example, they are back in their youthful days in that first week of life when they were able to do this unprompted.

This is a hard problem. I can summarize it in a few words, but let's just be honest about what we are asking in terms of what needs to happen to make regeneration happen.

Let's consider an analogy of a place like Manhattan. Manhattan relies on a very complicated infrastructure.Think about all the different things that have to be happening to keep the city functioning. We've got the water system, transportation, power, all of that has to work. Now say there is a natural disaster. If a blizzard or flood came, all of these systems would be impacted in certain ways and you would need to coordinate across those different groups in order to get the city back to its functional self.

Likewise, if we are going to repair the ear, we need to figure out all the different events that happen and coordinate among them. And for this to happen we actually need to coordinate it ourselves. Understanding anyone of these events can take a lifetime in one lab. If we really want to figure out a way to regenerate hair cells, we need to do better than that. We need to coordinate across species, across cell types, across systems and really push innovation.

That is where the HRP comes in. The Hearing Restoration Project is a consortium and this is a group of 13 researchers at universities across the United States and Canada. The way we differ from other scientific groups is that we are cooperating in a very free way to try to get our science to move forward collectively where we focus on studies that really leverage the power of collaboration. We prioritize any kind of project that is best done by a group of people versus anything else we can do individually in our labs. We also have a high priority of creating tools and resources that will accelerate research not just by these 13 labs but by anybody who has an interest in this.

Today, Dr. Hertzano will show you one example of a tool we supported the development of that I think is just a wonderful example of what we are trying to achieve. We also have a big priority on innovation. We are willing to try things that maybe we are not sure will work but it's worth giving it a try because the payoff is so great. And we have a system that promotes cross fostering of data and ideas early and often. We meet very regularly. We make sure through some of these tools created we can share the data well in advance and not wait around for all these other things to happen before we can make use of that data.

These are all the members of the consortium and it's truly a privilege to get to work with such a wonderful group of people who are all brilliant in the science that they do and

thoughtful and generous in the time they spend with each other and with the members of their labs that they are training who also go on to do wonderful science. I think you could not ask for a better group of colleagues to try to make something special happen.

As a group the HRP has come up with our strategic plan to see how we can collectively advance efforts for hair cell regeneration. Our first goal is to catalog the expression of thousands and thousands of genes across cell types, hair cells, supporting cells and across species—mouse, chicken, zebrafish—to find those pathways, sets of molecules, that are associated with regeneration or its failure. For example, what are the molecules that make supporting cells and regenerating species know that they have to divide to produce a hair cell? What are the molecules that ensure that a hair cell can integrate into the remaining epithelial, for example? This is basically defining the language we need for regeneration.

Then we can use a mouse model system, for example, and figure out what happens when we manipulate these pathways in the mammalian ear and get a sense of how far can we get. And again, this is a matter of testing things and figuring out what goes wrong and how we can make it better. This is an iterative process. As we identify the pathways and figure out how they are reacting in the mammalian ear we can design things to have the same effects. That would be the ultimate goal.

So, towards this big picture plan. How do we actually do this? We support a lot of data collection. Consortium members are collecting huge amounts of data from many species, where each lab is using what they know best to generate data they can share with everybody else in the consortium so we can compare, basically compare pathways across the systems and understand the problem. Figure out what is happening and use that information to devise a solution.

At the same time we are invested in generating tools and resources that will allow us to extract meaning from all of this data. That includes the gEAR, which is shown here and this is what Dr. Hertzano will present. This is a database where everyone in the consortium, in fact, anyone who has data to share can upload it so people can make quick comparisons on their own.

We also invested in a lot of computational analysis of the data to try and go beyond the biology and use computers to pull out information that you cannot get just staring at a list of genes. I will say I like staring at a list of genes and I have learned something on occasion. And in addition we are making and testing prototypes. As I said, we are willing to try things and see how far we get and use information about how far we get and go back

and inform our research again.

Another important part of our model is the teamwork. That is what I started out with by saying that's how the consortium differs. In fact, everybody in the consortium is part of the working group that is a smaller collection of people that work together to do the experiments, compare notes and meet on a regular basis so everybody's on the same page all the time.

And then in addition to that the whole consortium will meet to share data across working groups and share ideas across those groups.

We also have an annual meeting where we all come together and really think about what did we achieve this year, what do we want to do next? And brainstorm new ways to do it. We are constantly checking in with each other making sure we are doing the work in the best way we can.

And we are very grateful to get additional input from a wonderful Scientific Advisory Board to make sure we have thought of everything and it isn't somebody down in the weeds but can stand back and look at everything and has a chance to weigh in and make sure the work is going in the direction we wanted to go.

Those are kind of the overall goals of our group. And what I want to say is the future really is bright. I think that, you know, it is quite plausible to say yes, we can stimulate hair cell regeneration and this is a reasonable way to go for a prevention and treatment of hearing and balance disorders.

Why am I optimistic about this? We are learning a lot about these pathways. We have discovered things already. We are starting to get a sense on what is stopping or starting recovery. As we learn more there is just opportunity.

I think it is just a matter of, you know, continuing to do the work that we're doing and then we will see and discover these therapeutic terms. When will that be? I know that is what everybody would like an answer to.

The thing with science is what we can do is just keep doing the best work we can and know we will recognize the answer. It's very hard to predict. I will say we have a long way to go but we have every reason to be optimistic and I think we can get there as fast as possible because every day it seems that somebody comes up with a better way to do science and we are very quick at taking those opportunities and accelerating our own

work. In fact, the things we are doing now are using technologies that did not exist when the consortium started. While it is a complicated problem and I don't think tomorrow we are not going to have the answer, we are doing all the right things to get to the answer and I am really optimistic we will get there soon.

With that, I want to say thank you very much for your interest in this and I am definitely happy to take questions, but first what I would like to do is hand things over to Dr. Hertzano so she can tell you a bit more about what she has been doing through the HRP to produce a resource that, as I said, is helping not just members of the consortium but really anybody with an interest in hair cell regeneration.

I will give the screen to Ronna now if you are ready.

>> RONNA HERTZANO: Thank you, Lisa. It's great to be here this afternoon with my colleagues and friends. Dr. Goodrich, Dr. Anil Lalwani and Hearing Health Foundation and you, our supporters. I'm a surgeon-scientist. It's not an easy path, I am very busy. It's also difficult to convince people you can do it and that you are a worthwhile investment. In that sense, Hearing Health Foundation played a critical role in enabling my career as a surgeon scientist.

You can see here after getting a small resident grant for two years, Hearing Health Foundation actually funded an idea that I had on how to actually be able to analyze gene expression and different cell types of the ear without using complex models. This really lead to additional funding that allowed me to establish everything I do today. And coming back to HRP as sort of a senior member was a delight.

I think one of the greatest things about the HRP, as Dr. Goodrich said, is the fact that we use this combination of expertise. We use something that is called comparative genomics. This is the ability to compare how genes are expressed or regulated across species to reveal the secrets of hair cell regeneration.

You can imagine that a researcher that is an expert in chick biology or in zebrafish biology; they are different researchers. They grow in different worlds, in different labs. But having their knowledge in silo is not enough. And just to demonstrate to you how far behind the field was and how close we are now thanks to the consortium. We all know that all of these species have hair cells and supporting cells and roughly what do their ears look like. Until now, we were never able to say supporting cell A in the chick is the closest neighbor or the equivalent of supporting cell D in human or supporting cell F in zebrafish and now because we know these things we can start to build a map and build a blueprint that will

allow us to come up with ideas of drugs that we can use to induce regeneration in these species that do not regenerate.

We are very close to doing that. And, in fact, one of our strategic plan goals for this year is to come up with a paper that will map the hair cells as far as this goes. But how do you get researchers to be able to see these data across all these species? These are very complex data. These are massive data sets.

This is an example here of a dataset from Stefan Heller's lab that shows expression of a certain gene in a chick. You can see that's expressed in these cells that are hair cells and there are different types of them. And then from Dr. Piotrowski's lab the same gene has a different pattern because the hair cells are only this group and if it's colored red it means it is expressed.You can see already there are differences. This is another dataset from Dr. Heller's lab, and another set from Dr. Dabdoub's lab that's actually more similar to chick.

The idea is using this vast amount of data and we need to be able to see everything in one page. What the HRP has been doing, it has been supporting an idea that we had and is really allowing us to develop it to support the consortium. The consortium served as a focus group to bring this tool as it is developed in real time before publication and make it a main go-to in the field. Which is really neat because when you think about it and research and almost anything in life first to develop something, then you publish it, then people can use it.

With the HRP and the very strong knowledge that this is funded by the HHF, there was not a worry of funding. And we were able as we are developing this amazing resource to share it in real time with the entire community and advance discovery.

What this tool is is it allows you to put in a gene name and then immediately comes up with multiple datasets as you choose and it shows you the expression of that gene and the different data sets and there are more than 100 curated datasets. They are all from the ear that are public and they are organized according to topic. There are more than 800 data sets just to show you how many people use it, most of which are private.

The tool gives you information about the gene you are looking at. It provides additional information. If a gene causes hearing loss in mouse or in human, and it will light up a button. It turns out there are more than 1000 genes that when we cause a mutation in them, they will cause hearing loss in mouse or in human and it is impossible to remember all 1000 by heart. So this is very useful. The tool allows us to learn about any dataset or go to for publication.

It allows us to take any dataset, for example a dataset that compares expression and hair cells and supporting cells and turn into an instant graph and ask to see genes that are high in one population or low in another. Relook at all kinds of other research questions that are important in order to develop hypotheses.

We have additional options in a new age of omic gene expression called single cell RNA-seq we take the tissues and now instead of taking the tissue and sequencing what genes are expressed in the tissue we now take the tissue and sequence every single cell separately and impact. The HRP has been a pioneer of that in the ear. You can imagine how important that is because the techniques used previously were like taking a class that has 30 kids and averaging their score after every exam to determine if a specific child did better.

This technique is like getting the score from every single child separately. We are doing it at the single cell level for all the organisms and really being able to identify all these very small populations to really find what are the cells that are similar and are we missing cells that are necessary for regeneration in one species? Do we need to create them? Are the cells the source for regeneration in one system that are there and are not responding to a certain signal and if that is the case what drug based on for example can we add?

And then we have a team, like Dr. Goodrich said, they would do that with the gene editing, they will do that with trying drug delivery, they will do whatever is needed. And the tool allows gene browsing and so on and so forth. The neat thing is it is used now as a catalog in the field. So much so that as of today we have more than 100 data sets and public profiles, more than 1200 registered users of the gEAR, and more than 1000 monthly entries for research.

An important feature of the gEAR and what HRP and HHF was that it really encouraged teaching. If you make a tool and you do not teach how to use it, it is not useful. What we have done is with the support of the HRP and HHF, we have been going to every single large ear meeting and doing hands-on workshops and teaching individuals for 90 minutes, for shorter sessions or longer sessions how to use the tool that we developed. We have gEAR swag we get people to take home. We offer private sessions to labs. We offer private learning. We have a help desk. We do all of these things because in the HRP we think data sharing is important not just inside the consortium but that it is important across the board and, in fact, the papers we generate are based on data that is not just generated by the HRP but also people from the ERG or any researcher anywhere in the world.

Finally, I'm really excited to share that the gEAR actually did get published -- this seminar's

very timely -- it got published in Nature Methods, a high-impact journal just on June 25 a couple weeks ago.

And I will be remiss if I did not thank my team of collaborators. Anup Mahurkar and Seth Ament. Dr. Ament is a member of the HRP and he is one of our lead analysts. Joshua Orvis is the father of gEAR. Dr. Song supports the help desk. I can't say enough to thank the HRP and HHF and you because this has transformed things in the ear field and would not have been possible without your support.

ANIL LALWANI: Dr. Goodrich and Dr. Hertzano that was wonderful. I especially enjoyed your analogy to New York where I live and the complexity of the system. And along those lines, given the complexities, if you could have hair cell regeneration, will that lead to hearing or do these synaptic junctions, auditory nerve ,and sensory auditory processing need also need to be fixed for a human to hear? And that's from Dr. Daniel Fink. That's a really good question. You are muted, Lisa.

LISA GOODRICH: That is a great question and it is something I think about a lot. What I did not get to say was that my lab mostly works on the auditory nerve and on the spiral ganglion neurons. We have thought for a long time about how the hair cells are innervated by the spiral ganglion neurons and actually the supporting cells play an important role in that, not just the hair cells. What I can say is there is a lot of evidence that in the mouse when you can create hair cells in a place they are not supposed to be, the spiral ganglion neurons will follow and they are pretty good at sorting out and trying to find a target to innervate. I think there is a very good chance that if you made a hair cell in the right place it could get innervated and the neuron is already connected to the central nervous system and will be there and ready to go. So, of course, it will depend on why the hair cells are lost and what the state of the spiral ganglion neurons is but I think in many cases they could be connected in a functional way.

ANIL LALWANI: Ronna, did you want to add anything?

RONNA HERTZANO: I agree 100%. We see it also at the early phase of the cochleas is very permissive which is a little different than what happens to the mature cochlea which is what we deal with with age-related hearing loss. We know that when we regenerate hair cells early on in the permissive phase we do get hearing.

ANIL LALWANI: So, Dr. Goodrich, I think you also made an important comment I'm just going to echo again. This project is called Hearing Restoration Project; it's not called hair cell regeneration. As you pointed out, while the hair cells are important, there are lots of

other components of the inner ear that are also important for hearing and they all have to be taken care of. I think that was an excellent point and I just wanted to echo it again.

Kevin Richard also asks whether hair cell regeneration restores all frequencies and will these hair cells restore comprehensible audibility? It's a nice extension of the last question that is once you put everything together would you be able to understand words or not?

LISA GOODRICH: Again, it is going to be step-by-step. First we are trying to get hair cells. But Dr. Hertzano referred to the fact there are different kinds of hair cells and they are quite different across species. And species hear in different frequencies. Part of what we are trying to do is understand how to make just any hair cell but how can we start to generate hair cells that are going to be, you know, the right type and eventually to be just the right frequency. I think, and in fact, Dr. Hertzano's lab has done important work along this line in determining different kinds of hair cells. I would say first thing first, let's make some hair cells. And then, I think we will learn through that how perfectly tuned they need to be for there to be a measurable effect. I think that is something we can guess about but I don't think we have any way of getting a firm answer right now.

ANIL LALWANI: Great. I will paraphrase the next question a little bit asked by several of the attendees including Lillian, Karen and others. Let's say tomorrow Lisa and Ronna you identify gene A, the one we need to restore, what are some of the impediments to us taking the next steps? Whether it's clinical trials, can you talk to some of that and maybe a timeline that if tomorrow is the day you identified something, what does that look like, what does the intervention timeline look like too?

LISA GOODRICH: It depends. You say if you “identify” -- it depends on what identify means. If it is a candidate, that's one thing. If it is something that you have shown has an effect in an animal model, that's a different thing. If it’s just a candidate and someone does a comparison on gEAR and says “hey, you should really look at this gene,” we have to do due diligence in our science. We would go back and test it in animal models and we would try a bunch of different ways of manipulating the gene. If we started to get encouraged we might start to look for in vitro ways to develop drugs that would do the same thing or we might think about gene therapy depending on what the gene is. There is a lot of work you would want to do to make sure this is working the way you think it is and you're not actually in trying to fix the system introducing an additional problem. It would be the same in the development of any drug. You want to first prove you can solve the problem and then you want to make sure that in solving the problem you're not creating new problems. That is why clinical trials take a long time and you need to collect a lot of data and really see what is happening. I think the other impediment and I would like Dr. Hertzano to weigh

in on this as well is from a clinical point of view is delivering these things. That is going to depend again on what is your delivering and how often it needs to be delivered. But the ear does have challenges for delivery and so, that would be another kind of level of development that it would have to go through. Maybe Dr. Hertzano has other things she would like to add.

RONNA HERTZANO: This is great. These are great questions. It's fun. We are taking such a complex topic and we are trying to think about it. You know, the first thing I think when we think about timeline is how do we bend hearing loss? To realize hearing loss is not one disease. So there is the genetic hearing loss, a child that is born deaf and they are deaf because of mutation in gene A. So hearing restoration for that child will mean returning that missing gene.

That is really in advanced stages and there are several companies, even neighbors of Dr. Goodrich that are up for clinical trials for these genes. The beauty of it is it's probably going to work. The limitation is that it's going to help very few people. Because these individuals that have mutations in the specific genes we are looking at right now, and we are not looking at them at HRP are very rare, it's a very small proportion of the genetic hearing loss.

The second group is going to be let's talk about age-related hearing loss which is the most common problem. Every other person age 70 should be using hearing aids. And then, there the question is what is age-related hearing loss and is it a monogenic disease? Meaning is it caused by mutation in one gene? In some people it might be. In some people it might be a mixture.

Our hope in the consortium, in the field, is if their ears held up for 70 years maybe if we regenerated their hair cells and they got new ones they will hold maybe not 70 years but they will hold another 10-15 years and that will get them good enough without having to figure out the gene that is missing. And so, just as Dr. Goodrich said, it is a multistep process. Every step opens the door for something else. So at the level of gene delivery we have three teams working on gene delivery and HRP. And it very well may be some of the things identified will contribute to how some of the clinical trials are going to change, morph and do better. To Dr. Lawlani's question, "identify a gene," there may be a gene we can add to the cochlea to prevent the aging. And then we do not need regeneration. Maybe then the consortium switches its path to maintaining a healthy cochlea people age 40 and above. It's just a great journey.

ANIL LALWANI: Dr. Hertzano that's a great thing. Some of the people also asked about "Is

it possible to maintain hair cells and maintain hearing?" The answer is clearly yes. Some of the things you discover are, in fact, preventative as opposed to after-the-fact. Along those lines several have asked whether hearing loss is the only thing we can address to this project or are there things like tinnitus or hyperacusis or Ménière's disease? If you could take that specifically, that would be great, either one of you.

LISA GOODRICH: I will start by saying that the hair cells in the vestibular system are very important as well and that maintains your balance. That would be one obvious target for generating those hair cells. Tinnitus, which I actually suffer from so I really feel for everybody, it drives me crazy. It often starts with injury to the periphery. But just restoring the hair cells is unlikely to just make the tinnitus go away because that is a response of your central nervous system to the damage that happened. So there are parallel efforts that are attacking the tinnitus. There may be situations depending on why one has tinnitus where you could fix both things at once but I think they are biologically different problems. Ronna, would you like to add more clinical [insight]?

RONNA HERTZANO: You are right on. Really, one thing that is important to know is it is extremely rare to have tinnitus without hearing loss. When we are born we hear up to 20,000 Hz. As we age, we lose the high frequencies because sound comes into the ear from the base of the cochlea where the higher frequency detectors are. You can Google how old are my ears and find out how old you are. Hearing loss is not something private for a group of people that have some kind of mutations. Hearing loss -- you are human by having hearing loss and as we age and have more hearing loss, all of us have tinnitus. If we take anybody and put them in a complete soundproof room we can elicit tinnitus in almost everybody. If we just keep them in the anechoic chamber long enough. To answer your question, Dr. Lalwani, if we focus our efforts by preventing hearing loss and now HHF has a beautiful campaign to prevent exposure to loud sounds we will significantly decrease tinnitus. But just as Dr. Goodrich said, once you have the tinnitus it is not maintained anymore by the cochlea. It's maintained probably by the cerebellum and the brainstem and that's a different ballpark.

ANIL LALWANI: We have an interesting question for both of you even though I don't think your talk focused on this. Nancy and others ask about stem cells and their role in potentially hearing restoration, hair cell regeneration, or anything. You can take that question broadly and maybe address that.

LISA GOODRICH: Do you want to start this time or do you want me?

RONNA HERTZANO: I can, though I think you know more on stem cells than I do. Stem

cells are a great question. When I started hearing about stem cells, what I imagined was that we are just going to be dropping stem cells into the ear. Maybe not really pipetting them but maybe injecting them and all of a sudden everything is going to grow back and that's clearly not possible. The fluid milia out of the ear is completely toxic to cells that are free floating and cells need to integrate so that's not going to be the role of stem cells. We use stem cells to learn on how to direct the tissue that is there and there is this assumption, this is probably true because it's true across almost all tissues, there are what we call resident stem cells in the tissues that are sitting there and waiting for the right signal. If we can wake those up and make them do the things we want them to do, then we will be able to unlock regeneration. So the HRP does a fair amount of work with stem cells, specifically the lab of Dr. Edge and Dr. Heller. And I believe that is much of what we are using it for. I will pass it on to Lisa.

LISA GOODRICH: I agree. One thing I want to add is that actually the supporting cells, they are kind of stem cells. If you look at the morphology of those cells, if you look at the genes they express, they have a lot in common with the population of cells in your brain that actually produce new neurons when you need them. OK. There's something about those supporting cells that early on in life they have a lot of potential. One of the reasons why I have a lot of optimism for hair cell regeneration is it is not just that the supporting cells are conveniently located for generating hair cells, this is kind of what they do, okay? This is just getting them to relive their youth. This is what they started out doing. A lot of it is about reawakening that. If you think about many of you may have heard about the Nobel prize-winning work where Yamanaka discovered a few factors you can add to the cell to kind of turn it into a stem cell. And that has been very powerful. It is the same thing. If we could find a just few factors to convince the supporting cells in a mature ear to become stem cell-like again, I think that is the best opportunity for using stem cells. To really leverage the natural biology.

ANIL LALWANI: This kind of reminds me about 10-15 years ago I went to a seminar on stem cells expecting all sorts of therapeutic talks and pretty much 90% of it was on development and embryology. This is what you're talking about, both of you, the stem cells are ultimately telling us what kind of signals are necessary to recapitulate the development of hair cells. This may be for Dr. Hertzano. I'm going to make this a two-part question along the same line. One is if I had a cochlear implant, could I have gene therapy or hearing restoration? Number two, should I hold off on getting a cochlear implant waiting for hearing restoration therapy to come on board?

RONNA HERTZANO: Sure, I just came back from the clinic and people ask that question every day as they asked that question to you. The short and long answer of it is do not

wait. And it’s not because we do not think hair cell regeneration is going to happen. Hair cell regeneration will happen. Hearing restoration will happen. It's going to be a while before it happens, not at a level of a clinical trial for a specific mutation. And even if it is going to take in an optimistic timeline, 10 years, these 10 years are 10 years that it is important to hear. Cochlear implants do not provide natural hearing but they provide us with the single most important thing that we do as a human species, and they provide us with the ability to talk to other people, communicate, and stay part of society. They provide us with the opportunity to stay in the loop. Obviously there are deaf societies that communicate with sign language very well and they are vibrant and successful but there are a lot of people that are hard of hearing in the hearing world that do not have that type of support. And we can't afford to wait. Then I will answer two other things. One is, will you be able to get gene therapy later? Maybe. We don't really know exactly – it depends on what happens with the cochlear implant, but I will say one thing the cochlear implant does do: it maintains our neurons. It stimulates them with electricity. If we do not have the cochlear implant and we do not have any stimulation, those neurons that the hair cells or sensory epithelium as it regenerates will need those neurons will be gone and then we will not have something to transmit information. The second thing to remember is and why I am so optimistic about hair cell regeneration is let's think about what the cochlear implant does. Realistically we use around eight channels that use electricity, current spreads and despite that we are able to understand speech amazingly well. The assimilation of the implant is nowhere near refined or unique or elegant to what our natural hair cells do yet the brain does a lot of work for us and allows us to communicate.

For this reason, I think it almost doesn't matter what type of hair cells will regenerate. Maybe it will generate vestibular hair cells in the cochlea but if they will respond to sound enough and they will be sprinkled along the length of the cochlea then there is a good chance we are going to be able to detect and understand speech.

ANIL LALWANI: Dr. Goodrich and Dr. Hertzano, that was amazing. It is amazing what HRP is doing, what you all are doing in contributing to our knowledge. Our audience thank you so much for attending this very informative presentation by Dr. Goodrich and Dr. Hertzano on inner ear hair cell regeneration and the Hearing Restoration Project.

Hearing Health Foundation is so fortunate to be able to fund this urgent work with your help, you the listener, our attendees today. Remember you can donate to our efforts to advance better treatments and cures for hearing loss, tinnitus, any disease related to hearing and balance at hhf.org/donate. Well, thank you again Dr. Goodrich, Dr. Goodrich. Thank you again everyone for joining us. We look forward to our next meeting together. Have a wonderful evening.