

(Gwenaëlle Géléoc) It is my pleasure today to give you a summary of the different presentations we had during the scientific symposium related to new therapies and the work that is being pursued right now to develop new therapies for retinal degeneration and Usher syndrome.

So in my lab I actually also study Usher syndrome, but at a basic level. And understanding the role of the different Usher proteins, and also looking at how we can use novel technologies to recover hearing or protect the ear from degenerating and eventually collaborate with the labs that are focused on the eye. So today is a very exciting day for me, because we held this conference in Boston where I am from, working at Boston Children's Hospital in Boston. We held this conference four years ago. And there were maybe a handful of clinical trials that were on the way.

But today, four years later, the science has progressed so much that we have about 40 clinical trials going on. Not all for Usher syndrome, but all for retinal degeneration. And some more focused on Usher syndrome genes more

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precisely. And this is really exciting. But the other aspect which I want to touch upon is that there actually is the first clinical trial which started in 2006, was approved in the United States, the drug was approved in the United States in December 2017.

So when you think about Usher syndrome, and I don't have to reintroduce the basic of Usher syndrome, since Uwe did such a wonderful job, but as you understand there are at the moment at least we think of 10 genes which are associated with Usher syndrome. And many many mutations that affect the expression from the gene to the protein. So if the gene is disrupted, you may not get any protein expressed, or you may get a shortened protein, so a very short protein which will not be functional. And what we have learned through the years is that these Usher proteins form what we call an interactome, they interact with each other.

You can imagine a tree of Usher proteins that are assembled and play a role, structurally and functionally. If you take one of these proteins out, that tree falls apart. The sensory cells of the ear will eventually degenerate. The photoreceptor cells of the eye will eventually degenerate. This is what's going to lead to deafness and blindness. So where can we interfere with this mutation? How can we go beyond that and restore functions?

So there are lots of different approaches, many of them which are associated with - okay, a little bit more slowly. I'm sorry, I tend to speak fast. And I am French, but I

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speaking fast in French and in English. So we can think about what we call gene augmentation therapy or gene replacement therapy, in which case we basically add more copies of the normal gene. There is current work going on looking at gene editing, so using small molecules or different novel proteins that have been discovered recently to correct this gene. We have potential correction of translation, and I'll talk a little bit about that, which basically allow for correct reading of this gene sequence.

Right? Like you are reading a book, and instead of reading the word with a spelling mistake in the middle, you are actually going to correct that. Or there is a slow progress looking at molecules and using pharmacology mostly to limit the degeneration of the sensory cells. So during the scientific meeting we had a lot of different talks: on gene augmentation therapy by Alberto Auricchio, Gene editing by Carla Fuster Garcia.

Some of those were invited speakers, and others were selected from the abstracts they submitted. We had work presented on antisense and translational read-through therapy - I'm going to touch upon that - and also looking at small molecules and pharmacology with Yoshikazu Imanishi and Alaa Koleilat, and also potentially using stem cells, mostly at this moment to understand the disease. That is a part of all these different put-ins, but also to derive stem cell organoids, so basically reproduce the retina or the ear in a dish from patient-derived stem cells. So from your cells we can learn a lot. We can put these stem cells and force them to become a mini-eye or mini-

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ear. It's not quite like your ear, but it's a system that we can use to tease apart those different molecules. And it's extremely useful, and we've learned a lot from it. So I want to start with this amazing story of this clinical trial which is not for Usher syndrome, it's for LCA. It was started in 2006, and it took about 10 years for them - Jean Bennett was one of the main investigators who was involved - to go from lab results and the beginning of a clinical trial to a drug that was just approved.

So that was approved on December 19th, the drug is called Luxturna, and it is, basically what it does is gene augmentation therapy. So it allows to give back the normal copy of the gene for patients who are affected by Leber's congenital amaurosis or LCA, which does lead to retinitis pigmentosa, which is also something that we see in Usher syndrome. And I'm not sure if this is going to work. I'm going to try to play this. We have the sound, right? Let's see if it will work.

(Video) LCA stands for Leber's congenital amaurosis. It's a rare form of retinitis pigmentosa...

(Gwenaëlle Géléoc) Ah, it's not showing. Do you know how it can show?

(Video) Usually the babies are significantly impaired, and it's devastating, because not only is their vision terrible at birth, but it gets progressively worse with age, as the cells in the retina die off. A dog born blind with these very same conditions. So the puppies that were born blind

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cannot see their way around the room. (Video has stopped)

(Gwenaëlle Géléoc) The video is not showing, we're going to try to... It's not... Yes, okay! Should I start from the beginning? It's only a minute and a half.

(Video) LCA stands for Leber's congenital amaurosis. It's a rare form of retinitis pigmentosa, which is a progressive blinding disease. Usually the babies are significantly impaired, and it's devastating, because not only is their vision terrible at birth, but it gets progressively worse with age, as the cells in the retina die off. A dog born blind with these very same conditions.

So the puppies that were born blind could not see their way around the room, and we tested the possibility of restoring vision for the puppies by delivering the normal copy of the gene which is defective. That's called RPE65. And lo and behold, these dogs began to see, and so those results led us to propose to test this same approach for treating blindness in young children.

For these individual patients it's so gratifying to see what they now can do that they could not do before. There are two things that are really going to be important from this. One that we will move forward with this particular disease and get approval for the drug that we've been developing. The other outcome that I think is really important is that this could be a steppingstone for developing a treatment for other blinding diseases. (end of video)

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(Gwenaëlle Géléoc) Let's see if I can go back to my presentation. (sound of another video)

Oops, sorry! (sound of another video) Sorry! Sorry about that! Technical difficulties. Thank you. Okay, That's all right. Sorry about the technical difficulties. Now I went too fast. Okay, so I have about 10 minutes to go through the scientific presentations we had, and I apologize to the speakers who are here, I may have to go quickly through your slides. But one story that we heard during this meeting is actually a very important progress that we've made in the labs, because one of the issues with some of the Usher genes that we've been looking at is that they are too big to fit into the tools that we currently have.

So we have to design alternative strategies to package basically these genes to re-express the correct proteins. And so one option that we have now and that's really becoming, it's working quite well, is basically really chopping the gene into little pieces that we can package into our little vacuoles, and then provide them to either the eye or the ear. And so it's basically chopping in this case, this is an example of chopping the gene into two pieces, and having little pieces overlap, and then we can get reconstitution of the gene and expression of the protein in the cells.

And so this work was presented by Alberto Auricchio from Naples, Italy. And he validated the use of this dual, we call it that dual adeno-associated viral vectors. It's a virus which is innocuous, so it would not make you sick, it serves really as a vacuole to bring that gene inside the

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cell. And in this case Alberto was targeting the USH1B gene, which encodes for MYO7A. And so he showed that he could get the gene into the retina of pigs and get the gene expressed. And he also showed that he could get recovery of the morphological feature of the retina.

So while the mutant mice, for example, here that he was using which I call shaker mice, it's a model again for USH1B, while he was seeing mislocalization of structures called melanosomes, he was seeing accumulation of rhodopsin. But when he treated with this dual vector, he saw recovery of that morphology. So it's very encouraging, and we think that is going to be, you know, really changing the way we think about treatment. We'd end up often being the most affected, because there are a lot of more places where those mutations can occur.

That's the case for example for USH1B, that's the case for USH2A, and USH2B as well. So, yes so that's just the recovery of the morphology. And the goal is really now to go to clinical trial, so Auricchio told us a little bit about the work he is doing, developing a clinical trial using a dual AAV viral vector to target this MYO7A mutation. And they are working together with the Foundation Telethon and have a lot of participants which are involved in the development of this clinical trial. So that's one story.

The next story I'm going to talk about briefly is work done by Jennifer Lentz. She's from Louisiana, and she's been seeing and working with patients who all are affected by a specific mutation in the USH1C gene. And these are

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patients, they actually are French-Acadian patients from Louisiana. And what this mutation in the gene leads to is the expression of a very short truncated protein.

So instead of the very long protein which is called harmonin, in this case she sees a very short protein which is not functional and in this case leads to retinal degeneration and hearing loss as well. So what she designed here is to bypass this error that she sees in the gene, is to use something called antisense oligonucleotide. And again this is to skip that mistake in the reading frame of that gene, and it actually is very potent, it works very well.

And she demonstrated a few years ago, that by injecting this viral vector into mice that she designed to have that exact same mutation that the patients had, she can recover vestibular. So the mice have a normal vestibular behavior, they recover hearing, and they also recover vision. So I actually worked together with her at the different ways to apply this drug in a systematically or locally transmembrane application on a transmembrane or through the round window. And she is now working on the vision using local intravitreal injections. I'll just show you this quick video, I hope this time it will work well. So what we are looking at, it's very interesting, and I know a lot of you suffer from these vestibular balance disorders, and in the mice it's pretty pronounced.

So when a mouse has the mutation in Usher 1 gene, it's typically associated with a very typical behavior of repetitive rotative movements, very active rotative movements.

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You'll see that here. So here in this case on top we have two controlled mice. One that was injected with inoffensive drugs, and this one was injected with control drugs. And then this one was injected with the antisense oligonucleotide, we call it ASO29, and then a mutant, so this is the one I'm really going to be looking at. A mutant that's not treated, and a mutant that's treated.

And now you can look at their behavior. So you see the mutant mice are really spinning, you know they rotate like that all the time. And in fact they actually are typically a lot leaner because of that, they are very active. But you can see that this mouse that was treated here really behaves like the normal mice. They are rotating, they are moving around the chamber, but they are not doing this repetitive motion behavior.

And so any of the treatments that we've done, local or systemic, really led to this recovery so it's pretty pronounced. We also saw recovery of hearing and recovery of visual function. I won't have time to really go through this data. But it's very encouraging. Okay, so I'm going to have to go a bit more quickly, so this is - no I mean, not quickly but just skip some slides, that's what I mean. Not to speak faster. Don't worry. I just won't tell all the stories that I have, but I will try to skip and to keep it slow. Erwin from the Netherlands is looking at again the same kind of approach using antisense oligonucleotide, and this is here for Usher syndrome 2A. And he has validated his approach in zebrafish and also patient-derived photoreceptor progenitors.

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They are actually starting a clinical trial with a company called ProQR, and they started a clinical trial to target LCA. In the process of starting a clinical trial targeting mutation in USH2A. This one should be starting by the end of this year. So it's very very encouraging. Kerstin used a drug, I call it TRIDS, they target in-frame nonsense mutations so this is a typical aminoglycoside, which in this case do not induce hearing loss, but also can allow correct reading frame. So this is also a drug that's been very promising and importantly again that she validated in patient-derived fibroblasts.

You guys are really part of this science, you are part of this progress. And the patient cells that we can get to work on in the lab can really bring us, you know, many steps further. That was really evident throughout our talks, so for anybody who has doubts, this is really important for the science and eventually for the development of therapies. And again there is progress with the use of these drugs that she has been studying, and she is really hopeful that there will be a clinical trial very soon targeting Usher syndrome. Finally, I will finish with a short story about retinal organoids. And so again this is using stem cells and using them to make a mini-eye and eye cup in a dish. And again this has been very informative.

Mike Cheetham from London reported a lot of his exciting work looking at the development of retinal organoids as the disease model. Not only to understand the disease, but also to assess different drugs and in particular, for example, small molecules to restore the maturation and

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limit the degeneration of the photoreceptor cells. And so there was also a story from Yoshikazu Imanishi from the US, which again is assessing different molecules.

He has a system for screening a lot of molecules on these tissues, to really find molecules that are non-toxic and can really have an effect on the photoreceptor cells and then assess those drugs really in the mouse. So I will wrap up by saying, the future is in our hand, it's in your hand, to shine a light on Usher syndrome we need you. As scientists today, this day, this meeting is so important for us, it's so important for us to know that what we are doing matters, and for me to see where we've been from four years ago to today is absolutely mind blowing.

And I know when we see you again in three years - hopefully - it's going to be again another story, and it's really wonderful, and I thank you for being here. And I want just to finish with the main thesis of Usher syndrome. There is a lot of us, and I now it's not everyone, it's just some of us here. You are not alone, we are not alone, we are all working towards understanding the disease and finding a cure. Thank you. (applause)