USHER SYNDROME FAMILY CONFERENCE
JULY 11, 2015

MARK DUNNING: The registration is open now and if you have not gotten breakfast yet there's breakfast over there. And the bulls are outside, so if you look out the window you will see the bulls running for their lives.

If you have any teenagers going on the field trip they can meet over by the piano. Over by the left there's a piano. They can meet there. And if you have younger kids they're going to be in the day care on the second floor so if you need directions let us know.

Hello everyone. We're going to get started. Thank you all for coming. This is our 7th Usher Syndrome Family Conference (paused to change layout colors by request).

DR BAZAN: Thank you, Mark, and good morning everyone. I see a lot of people here that have positive energy. I am excited because they can give you some idea of what can happen and what your possibilities might be to work and help your family or you directly who have Usher Syndrome.

Usher's came to the attention of our family I would say maybe 25 or 30 years ago. I have a nephew who was born deaf. I already had an aunt who was deaf, so we didn't think it was usual. At the time there was a question of whether she had been born deaf or whether she contracted her illness at a young age that caused her deafness. Then, when my nephew was born, it became obvious it was a genetic trait and we would see more deaf children born in our family.

350 strong, and that's just on my father's side of the family. He was one of ten, and we've got multiple family units everywhere across the United States and other parts of the world to Usher Syndrome is a genetic trait in the Acadian family. So it was about 14 years later, when Baron was a young child, I was actually a member of the Louisiana Public Service Commission and we decided to take upon ourselves to create the telecommunications relay system in order to help the deaf community communicate with the world. At the time, there was no way for deaf people to order a pizza or have any interaction with the outside world. So my staff and I visually impaired people was part of our team. That was my first introduction to Usher Syndrome.

When I learned about the fact it was very common in Louisiana, in particular that some deaf citizens would also lose their vision. And it was a pretty shocking revelation to me, but more shocking as my nephew grew up to be older and complained about a lack of night vision. And then the diagnosis came. So we understood immediately what was going on. We learned all about that.

It was a really tough time because we have beautiful children in our family; and, as you know, we take our hearing for granted. We take our vision for granted. And we expect that that to be passed on to our families. It was a difficult time, but we learned there is so much talent in that individual and how to adapt and how to help that person fulfill their capacity. And of course, technology is wonderful and e-mailing lessened the need for the telecommunication center. Now my nephew could communicate with parents, grandparents, anybody. Just anybody across the world. He learned also how

to use computers and how to communicate through the technology. I guess the sad thing is he didn't have a cochlear implant.

It was a few years later when my beautiful niece Elise and her husband Briar had a second child. We have a large number of people born deaf in our state. So a law was passed that before a baby leaves a Louisiana hospital a hearing test is given, to see whether or not they have brain activity stimulated through noise. They were saddened that their child would have limitations, but they didn't take it as a handicap. He has been such an inspiration. They wrapped their arms around this child. Hunter is a highly functional non-hearing child. But they know he is subject to losing eyesight at some point. So our hope and the hope for all of you is that our scientists discover a way to block the transmission of the blindness and perhaps find a cure for all of it as best we can. I don't think that's impossible. We have seen miracles. My own mother had her eye operated on when she lost some of her vision in one eye and now she can see. There are medical miracles all around us. We as scientists can unlock the secrets of technology and give the quality of life to everyone.

And that is why I'm here, because we support coalitions to get to share. When we are dealing with something relatively rare, we feel isolation and the power of bringing together people with a common problem or situation is so powerful.

So, Mark, thank you for being inspired to send the message out across the nation that there isn't an isolation, that we can bring together some new ideas. And we can recognize the value of our lives and the challenges, and work together to be stronger people.

For all of that and my nephews, whom I love dearly, I just wish the very best for all of you to deal a little differently and have friends that you can share challenges through life. Because we are all in this world together, and sharing makes us a better people.

New Orleans is a pretty great place to be, and the Running of the Bulls was set up just for you. I think they brought it right here by your hotel. So it was a great idea to come to New Orleans. We have fine food and great entertainment. Here at the conference, you will learn new and important information. Our scientists are addressing the problem and looking for solutions. I believe we might all one day be enlightened and life will be better for all. Thank you for being here.

MARK DUNNING: You're at the LSU School of medicine so please join me in welcoming Dr. Bazan.

DR. BAZAN: Thank you very much, Mark, for this invitation. And just to start, I'd like to thank Governor Blanco. I met with her several times and she was an effective leader in our state in many capacities. Thank you for your support for research in Louisiana.

I want to ask you how many of you were from Louisiana. May I see a show of hands? Because as soon as I start talking you may believe I am from Lafayette. Let's get something straight. My accent is not Cajun. I am from Argentina. My family and I moved here many years ago, and we love everything in Louisiana. And very early on, I became impacted because of what Governor Blanco was talking about. Several neurodegenerative conditions. And we became very much involved at looking at

Usher in the early '80s. Our findings at that time was a starting point I would like to share with you.

I'd like to tell you why we do what we do in the cabinet, and first of all -- just disclosure -- I have had academic collaborations with Dennis Rice. He moved to Nogales and I've been lucky through my work to stumble on new findings that hopefully can be applied in the short term.

I'd like to share with all of you some concepts first. Concepts of which is the problem. How we, as I said, in our laboratory try to tackle these issues. We have as a consequence of life expectancy for the photoreceptors as reflected. Some do, some do not show it's a successful agent and unsuccessful agent. Can we as scientists solve particularly Usher Syndrome. Sight and hearing neurodegenerative condition. Regular development when our eyes are formed are given by a mechanism. And then photoreceptors become divided. So when looking at degenerative diseases, like retinitis pigmentosa, due to biology not whether a failure.

In our eyes we have a wonderful interdependent relationship between two cells. The one on the top here. Let's see if I can -- do we have a pointer? It's a cell that cups the photoreceptor and they are interdependent. These next few images I'd like to tell you the basis for my laboratory to design experiments. We have been asked about the molecular logic. Let's leave Usher Syndrome for a moment and like other, retinitis pigmentosa in this case. And based why the disease don't have latency early on. There are several years that the biology sustain with the forces of the genetic defect to maintain sight. So we suggested that there are we call them

(Can't understand the speaker.) We call do not exist in the brain. They are made in the meaning they are made as needed inside the cell for survival. And so we decipher this, I would like to share with you about the excitement. We have two findings this year. One is identifying why and how the precursor of this neuroprotective molecule is connected. When we ask the question why is -- what takes place inside the cell to implement survival. And there we observed a specific gene being regulated. We harnessed this new knowledge for scientific purposes. And, of course, that is the goal. As Governor Blanco said, knowledge is the gate that helps us translate into the needs of patients. The key is an Omega 3 fatty acid. In our cochlea, is the richest in our body. We can't make this molecule. It is a fatty acid that comes from fish oils. I prepared for you a summary of why this has been a target in the search of mechanisms. First, in the top enriched and very avidly retained and I think in the body, in faux receptor cells.

And in 2004, we found a recurrence of DPD-1 this fatty acid is necessary for early development for vision in the brain. The function of the retina in the brain. We in the early '80s discovered there is a shortage in this fatty acid in Usher Syndrome patients. It was in a paper in 1986 and several other papers also show a decrease in the blood the presence of this fatty acid. This fat is a building block. And these patients have lower amounts in the blood. But now we discovered the cell is allowed to form. We also found that early on in the disease, in the memory areas, it drops 25 percent. More recently, we discovered it is a precursor of longer molecules. This is the chemistry part for all of you. And I don't know if Mark told you, but there is going to

be a quiz at the end. The retina has an enzyme that makes this, going up to 34, make it longer and that is necessary for the function of the cell. And that longer version of the molecule is bound to production, mutations of these are so on. So what I told you is that when these RPE cells are created, they appear I think it was 1986 in Usher's. I think they said the mechanism that taught us. And then our laboratory uncovered how the acids go from one cell to the other. And this is actually the paper that came out a couple months ago. We found a molecule that always had an active receptor run. I have highlighted in blue and in black from Lexington and other places. We set up a team to look and ask the question. I just show you some of the science here. The first surprise was when we used different ways to, we have something also you know this one method. And this is another one with the gene cropping and they looked at the gene from mice. This is normal. They have a flecked appearance. And then looking beneath the retina, we found cells that respond to very subtle inflammation. And then we found that there were undigested pieces of the photoreceptor cell. Showing that we knock out the gene this, the presence of this under the microscope and what you see in the middle is the size of the photoreceptors are different. This evidence that early on two weeks after birth, the cells are dying in the photoreceptors.

I went to go a little faster here because I want to emphasize the concepts. What we have in the laboratory is the way to look at the retina. It's called OCT. This is a very basic way to use. If we look at a mouse of different ages, a normal mouse after 33 weeks. That's the perfect photoreceptor cell. In the photoreceptor you can quantify this and see how the photoreceptor. So of course, then we went on to see that another

element in the relationship between the cells is the vitamin A recycling. And sure enough, all of those components, when we knock out these proteins, see the cell can degenerate, we wanted to have more. This is something that we as scientists do often. All of this that I will show you demonstrates is that the animals without the protein have cell-selective DHA change. No other things when we delete the problem. And one big surprise was this long molecule. Here we express the protein and, sure enough, this protein decided to take the protein in and out of the cell. What is this protein? In this cell we have several proteins and the most known were G proteins. Several years ago it was discovered but not reported. The interesting thing is that this receptor is flipped. It has a different organization of the molecule. We went in-depth and built the first time the molecule. Using this molecule the protein to capture the fatty acid and we have an explanation of how the cell survives, essentially.

I want to tell you this is a very exciting receptor because there's a hormone that activates the receptor that has nothing to do with what we found. And so the DHA on the photoreceptor cell is necessary for vision. So these are the conclusions of what I described to demonstrate that this is essentially for vision. And then we found there is a genetic variant with mutations in the protein that we found. The second paper and the genes how these mechanisms are executed and what is discovered was the genes. The final slide I'd like to spend a couple of minutes reflecting. This is the title of my presentation. How normal molecular principles can be harnessed. As we learn, as we are learning through our work how the responses happen. Mimicking nature responses to onset and we are developing ways to deal with these. The only

one to supplement the diet. I have a friend at Harvard who had been studying the effects of vitamin A. And it's a complex situation because there are either elements.

We are testing other ways to bypass ways to reach the retina. We are developing, we have about 45 chemists working with us on this project. One is in Spain, one other is in California. We do the biology and point number two is to develop. Because we learned that they are precursors of the values to make them bioavailable. Modifying lipids and other acids. The creation of knowledge from a very basic point of view. We don't understand fully many mechanisms yet.

4th, they are evolving at a molecular level. So there's a communication between the neurosciences and others. Finally, obviously a combination of therapies. I'd like to name my colleagues that did this work.

(Please refer to slide.)

We continue intervention -- I'm very grateful to people that gave us funding for our work. The main one is the chair of LSU. They have funded our research since 1981. And there are NIH and several institutions that believe in our work and give us funding.

Thank you very much for your attention.

MARK DUNNING: Thank you very much, Dr. Bazan.

You have a couple of choices for questions. We take very frequent and large brakes so you'll have an opportunity to corner him. You will also have a chance to ask questions later on.

Our next speaker is Ben Shaberman. He's going to talk about saving the retina through neuroprotection.

DR. BEN SHABERMAN: Good morning. It’s wonderful to be here. A real pleasure. Former Governor Blanco is inspiring, and that's the way I feel about the community. I write about a lot of different diseases. But it’s this community that I've been most inspired by your courage, passion. It’s a pleasure to be here. I'm going to do some introductory slides that hopefully will help you with other presentations. Finally, at the end of the presentation we will answer the burning question: Can disco save your vision? An important question.

First of all let me tell you a little bit about my foundation. We have been around for 44 years. We have raised almost $7 million for research. I think one thing that's been important over the years is that we have funded in research that maybe other organizations were skittish about. Cutting edge research that was not -- that other organizations were not willing to. I think gene therapy is one of those. Others were staying away from it. We saw the opportunity in gene therapy to save the retina and I think you know now gene therapy is one of the most important ways to save vision. A lot of research in the U.S. We also fund a lot in Europe, the Netherlands, the UK, and France. What's important to keep in mind, it's important to look at Usher Syndrome as Usher is retinitis pigmentosa and hearing loss. That my in the short of long run help people with Usher Syndrome. And a lot of therapies I'll talk about in the slides are those papers. If they do get FDA approved, it may help this community. But again, it's going to be called RP research.

The best way to think about the retina is, it's like film in a camera. Obviously we don't put film in cameras but you can possibly remember in the old days. When light

enters the eye it gets refracted by the lens. It goes through the vitreous gel. Those signals are sent by a cable to the optic nerve and that's how we see. And the retina is an amazing piece of tissue. It's like wet tissue paper. For its size it processes more oxygen than any other tissue in the body. It goes through a regenerative process at night. So it's doing its work when we are asleep. So, this is a diagram of the retina. This is a what we call the layer cake diagram. The vertical cells in the diagram are the photoreceptors. The cells that convert the light to electrical stimuli. I find that remarkable for a piece of tissue a half-millimeter thick.

Cones are concentrated in the macular areas. And cones are the most important for our daily activities. They allow us to do detail-oriented work. They have they give us color vision. And in this diagram, there are the red, green, and blue cone-shaped cells. On the periphery of the retina are the rods. And rods give you vision in dark and they also provide peripheral vision.

That's just a little orientation to the retina, and then I want to get into the concept of neuroprotection. And this touches on some of the functions we already talked about. It's delivering a to keep the cells alive. And one of the most important aspects of neuroprotection is that it works independent of where a lot of these neuroprotective treatments that I may be talking about lie. It’s called crosscutting. To benefit from neuroprotection. And as Dr. Bazan said, neuroprotection is developed for Alzheimer's disease and Parkinson's disease, too. These are all neuronal conditions. But what's actually nice about the retina, it's a more accessible part of your neural system. It's

right in front and you can access it. So the retina is actually a nice target of development of neuroprotective approaches.

So, this is where I'll get into a little bit of deep science. To talk neuroprotection and different approaches. Different pathways to keep the retina alive. One pathway is the antioxidant pathway. Cusses is the wear and tear your body goes through like if you smoke and eat too much crawfish. Our bodies create by-products that are toxic and harmful, called free radicals, and researchers are looking for ways to neutralize the free radicals. Another neuroprotective pathway is trying to prevent apoptosis. Cells in your body will do this if they sense things aren't going well for them. You lose vision. Researchers are trying to explore ways they can prevent apoptosis. And the cells, we call these growth factors and I'll talk about a couple of treatments that lead to the production of growth factors and keep the cells alive.

Finally, all the cells in our body have mitochondria. They're the power supply. In diseases they do not work in full capacity. And researches believe this exacerbates the condition. So researchers are targeting boosting mitochondria. You can get it through an eye drop. That's the most elegant way. You can take it orally as a pill and you can also use gene therapies and stem cells to deliver. You'll be hearing later today about gene replacement therapies. You are replacing lost photoreceptors. That's what stem cells are used for in replacing photoreceptors. But not every treatment will work for anybody.

And in some cases, as some of you may know, gene replacement therapy may not be an option because they can't find your gene. That's why neuroprotection plays a

great role. Maybe you will get nerve protection and gene therapy. And when they find your gene, you can switch to gene therapy later in life. And if you're taking a treatment orally or through eye drops, a nice benefit there, if you need more or less that's easy to do. Once you get gene therapy, it's harder to reverse. So those have that advantage.

I'm going to talk now about a few emerging therapies we are excited about. We put more than $2 million in mitochemotherapeutics. They continue to refine it to make it even more potent. They are working on it in large animals now, and their last hurdle is to make a formulation to be delivered in an eye drop. And once they do that they'll go to the FDA. Some very exciting news is this researchers on the right at the University California Irvine have been given authorization to do a treatment. They are stem cells that developed this pathway toward the retina. And when they are injecting in the eye, they release a cocktail of proteins to help you keep your cones from degenerating. It works as a protein factor. He has authorization to launch a clinical trial. I'm not sure if they have injected that into their first patient or not.

Something we are also excited about is a protein called rod-derived cone viability factor. You probably are aware of the idea that your eyes are affected first because you lose night vision. As the rods degenerate, the cones follow. And these researchers in France, (pronounced French names) that's the best attempt that I can make, they discovered that rods secrete a protein that help keep cones alive. They are not replacing a bad gene but this gene therapy is making this RCVF to keep the cones alive. They're pretty close to a clinical trial. Once the gene therapy is injected into the

eye, it will replace to rescue cones. This should work in Usher Syndrome and any other disease trying to recover cones.

I just want to cover other treatments. The same group in France screened 700 plant extracts to find the specific molecules that affect cones. And that he is moving that toward a clinical trial. And I think the idea and to formulate it in an eye drop. And John Ash is developing antioxidative properties. He's still in lab studies but he is hoping to get in a clinical trial.

I'd also like to mention Mathew LaVail. He's been working on neuroprotection for decades. We sometimes call him the grandfather of neuroprotection. He is working on models to test gene therapies. We've funded him for a long time.

And finally I want to answer that question concerning disco. Can disco save your vision? Yes. I'm glad I could deliver good news. Our research team out of Emory in Atlanta found mice with RP, mice that exercised for one hour had slower degeneration. I don't have the slide up here but there's on Italian group that show mice with RP raised in nurturing environments, they have good bedding and mice friends, showed a slowing in the degeneration.

I recommend to live a healthy life, eat well, get exercise, and take care of yourselves.

Finally, some contact information. I'll being here to answer questions, but I encourage you to go to the website www.fightblindness.org. You can reach me at bshaberman@blindness.org. I hope you guys are familiar with the website clinicaltrials.gov. It was established by NIH and it has every clinical trial in the US.

And that's the good way to see what's going on in Usher Syndrome and other diseases. That concludes my talk. Thank you for your attention.

MARK DUNNING: Thank you very much. That was fantastic. It's good to know disco will save your vision. From an Usher Syndrome point of view we are looking to do an Usher Syndrome awareness day. Several of us are going to run a marathon in Alaska. We are also going to try to do a mile- a-thon we want everyone to participate in. We want everyone to sign up to commit to running a mile a day until September 19th, which will add up to the length of a marathon. That will be 25 miles, and on September 19th we want you to do those last 1.2 miles. So like Ben said, it's good to rehearse.

Right now it's time for a break. We will get back together at 10:30. We are actually on time. There are refreshments behind me, and I hope you take the time to visit the exhibitors. We'll talk soon.

MARK DUNNING: Since we're still on time, I would like to ask everyone to take their seats and we can get started again. If you could have people take their seats, we'll get started.

Okay I think we're set to get started. I hope everyone had a chance to network. That's a good sign. That's what we want. We want you to get a chance to talk to each other.

Right now it's my pleasure to frequent the next speaker Dr. Jennifer Lentz. A member of the Neuroscience Center of Excellence, and she is an assistant professor and an adjunct faculty member at the LSU Health Science Center, here in New Orleans. Please welcome Dr. Jennifer Lentz.

DR. LENTZ: Hello. There's a collection of water up here. You would think we ran with the Running of the Bulls this morning. Thank you for coming. I want to extend a thank you for Mark and especially Crista, who have done a good amount of work to bring us all together today.

I also want to thank the interpreters. And lastly I want to extend a thank you to all of you for taking time and making the effort to come here and be with us today. As science researchers, it's all of you that provide inspiration to us. We learn a lot from you and it helps guide our daily activities in the laboratory. I can't promise we are going to be as exciting at the outside. Our goal with give you a little bit of what we know for Usher Syndrome and then move into new therapeutic approaches, including translational read through small moticals. And also the nucleotype therapies and the future directions. Our overall goal, the scientists, the medical community, working toward progress is to provide tools to every individual with Usher. That's our overall goal and mission.

Since we want to be greedy, we want to give you tools to choose from. There are a number of strategies and approaches underway. The prevalence of

Usher Syndrome is an autosomal genetic disease. Autosomal means that it effects both males and females equally. One gene you get from your mom, one you get from your dad in order to have Usher. It is currently the leading cause of deaf-blindness. It is known to effect. I want to mention recently in the last few years there have been studies in children. I want to clarify that study was done in two pediatric populations in deaf and hard-of-hearing children. So the group mentioned was not the general population. So this gives us the idea that Usher Syndrome is both rare and common, depending on what group.

That's hard to think about, being both rare and common. Usher is both rare and common because if, for example, you are a doctor or a cochlear implant specialist at a hospital, you may see many Usher patients and consider it common. If you look at the world population and you are a community physician, you may not see a lot of patients. So you may consider Usher Syndrome to be a rare disease. A lot of significant progress has been made to identify genes that cause Usher. Type one Usher, USH one, USH two, and USH three. Recently there is a new clinical type coming to light called Atypical USH. And these patients have early onset hearing impairment and a very mild retinitis pigmentosa. So we are making more and more progress. Currently, there are 16 low side or places in into known. We've identified 13 genes, that if you have mutations in these genes, you can have Usher Syndrome. There has been one modifier gene identified. So if you have mutations in this gene, you have a different course, different symptoms, it modifies your clinical progression. This is

a current table. It lists the three types of Usher and the genes and proteins. We use numbers USH one USH two and USH three. What types of symptoms you have and when we may experience those symptoms and then we use letters to describe which mutation you might have in which gene. one, individuals with type one Usher Syndrome have congenital severe to profound hearing impairment. We abbreviate. You have vestibular arreflexia and it begins in early adolescence. There are six genes known to be associated with Usher one. Those are USH1A, USH1B, USH1C, USH1D.

And patients with type two Usher Syndrome, the most common type throughout the world, also have congenital hearing impairment, but it's mild in the lower frequencies. They have normal vestibular responses and it typically begins in late adolescence. The genes associated with Type 2 Usher Syndrome are USH2A, USH2B, USH2C and USH2D. And the last type of Usher is the most rare tape of Usher throughout the world. These individuals typically have a later hearing impairment and it is progressive. And they have adult onset RP. Some patients do have balance problems and some don't.

So I want to take a minute and talk about the proteins associated with Usher. All of these proteins are known to express in that then traveled to the brain, and that's what we experience as hearing and also been found in retinal photoreceptors in the eye. Ben talked a little bit about that as well as the 3rd type of receptor in the retinal cell called the Muller glial cells. These three cells act together and the current hypothesis is that de fact in one or all three of these

cells reduced the ability of the post receptor to maintain itself over time. So for Usher the current hypothesis is the development of the cells in the ear and photoreceptor maintenance.

So I want to take a step back and talk a little bit about the process that the protein is made. We have genes there are the code. Those are transcribed into RNA molecules which are the code. This process happens inside the cell and begins the nucleus. The chromosomes are made up of our genes and these genes are areas used in the code and areas not used in the code. So the first thing is the compliment used in the DNA, turned into RNA, a compliment. And the areas not used for the code are snipped out and the areas used are stitched together, called splicing. The final area is transported into the nucleus. The ribosome is a collection of proteins, reads the code and stiches together amino acids to make the protein. That areas undergoes other modifications to make a functional protein. We have a single gene that encodes for RNA molecules and because of that process of splicing there are lots of type of RNA molecules. Lots of different parts of the same gene are spliced out to make multiple, many forms of the protein. The making of the RNA molecule as well as the transport of the cell body or the making of the protein.

So there are typically three types of mutations. Nonsense mutations prematurely stop the reading of the protein. The ribosome is reading along that chain and causes the molecule to stop long before it should.

The missense mutation is one that changes one amino acid. It can affect the folding of the protein to change its function a little bit. There are mutations that affect splicing and mutations called insertions or deletions. These are added or missing pieces of the gene. So another current hypothesis for Usher Syndrome, there is no that suggestion a strong phenotype-genotype relation, depending on the gene or the mutation that you have and the phenotype or the symptoms that you have.

So for at least four of the Usher one genes, USH1C, USH1D, USH1E and USH1F, no normal protein is made. You have a type 1 Usher symptom course. That's the most severe type. Other mutations in the same gene have either mis-sensory slicing mutations that effect only some of the RNA, and these sort of leaking mutations make a little bit of the protein or a little differently but they are still make some protein. And those patients have hearing impairment only and not retinitis pigmentosa. This is really important because if we knew more about all the mutations that exist, we might be better able to predict your course of Usher Syndrome. This might account for some of the variability that we see.

Why some have more severe hearing impairment than others. There's a lot going on to understand the history or your course of Usher Syndrome and your particular mutation type. So I'm going to move on to into their mutic strategies.

There is a lot going on, it's a really ,really exciting time for Usher Syndrome. It’s not complete who that, which type of Usher might benefit from that. So the first type of strategy targets Usher in general. With any type of deafness or

blindness, it might work for any type. These include stem cell therapy. This is a process where skin and blood compel is given and those cells are turned into stem cells and coaxed into turning into hair or eye cells. This is a process that delivers genes that give light sensitivity to the light cells in the retina. So if you are missing light receptors, you are given a protein that functions in sensing light and targets the cells in the retina. There is a strategy that targets the mutation inside. Gene replacement therapy is a strategy that delivered a normal copy of a gene and later we'll get an update about the gene therapy replacement trial.

There two types of gene replacement therapy. Viral mediated gene delivery is the introduction of foreign DNA into cells by transfection, as well as nanotechnology being developed that delivers the gene.

Another type of therapeutic strategy targets a particular mutation type. So the treatment of any type caused by a missense mutation of USH1C, the most current estimate is one percent are nonsense mutations. So while it is week ago studies in a laboratory there is.

And finally, one new therapeutic strategy targets a mutation in a particular gene. This is caused by a very specific mutations. This small drug therapy would work for USH1C caused by a particular mutation, in particular, the N40K mutations in the USH1 gene.

So now I want to talk about the strategies in USH1C. I'm going to talk a little bit about the translational read-through inducing drugs. First, this is a diagram of the USH1C gene. These boxes here are the genes used to make the molecule.

These are parts of the gene not used. So those lines are then spliced out and the remainder of the parts being used are stitched back together.

So the remainder of the parts of the gene are stitched back together and these are the variance and these are used to encode for hormone and ice forms, the proteins encoded by the USH-specific splices mutations here in USH1C. It affects all of the RNA molecules and translational read-through drugs target nonsense mutations within USH1C. So the translational aminoglycosides are engineered in the laboratory that target the ribosome in the cell body where proteins made. What this drug does is insert a random amino acid to prevent stopping of the translation. If we look here, this is that molecule. The ribosome has come to read the code and it's stitching together amino acid to make the mutation. And the ribosome gets to that mutation and says stop translation at this point. It doesn't continue to make the protein. So what these drugs do is bind that ribosome and force the ribosome to change shape and not pay attention to that stop code. It pulls a random amino acid and makes a full length protein. Currently, these drugs are being tested in a laboratory in the USH1C gene but would work in any USH gene. Two different translational read-through drugs that have been tested that direct the mutations in the eyes of laboratory animals. Full protein has been detected. This is really exciting. Currently they are trying to develop a better model to test if this could work. It doesn't have the mutation in the genome, so the doctor has put in an extra copy of the mutation as well as trying to test the drugs on patient cell lines.

So now I'm going to switch and talk about the work in our laboratory and talk about the oligonucleotide therapy for USH1C in Louisiana, the founder mutation came with the Acadian population that settled in Louisiana. And if we look at the USH1C gene we notice that patients have a truncated USH1C molecule. An extra piece is spliced out of the molecule so the remainder molecule is short. This results in a truncated protein. So the first thing we did in our lab is to take the mutations and put it into a mouse. We noticed that in the ears and eyes of the mice, they have the same mutation. So we felt we had a really good model. In fact, the mice were hearing impaired at birth. They don't respond to sound stimulus. They have circling and head tossing behavior. They run in circles and have a balance problem. They begin to lose photoreceptors later on in life. So we developed an antisense oligonucleotide. It's 15 to 18 long and it finds that mutation and binds to it and prevents that faulty mutation. The idea is then for those there to be less truncated RNA and protein molecules and more normal RNA and protein.

So after we tested about 50 in the dish, in cells, in the test tube, we settled on one of them that gave us the most normal production. Typically in the lab is we treat our Usher pups that have the mutation either with the ASO mutation or a control or placebo and wait for a period. We test their hearing function, visual function, then at their hair cells and visual receptors in eyes. We look at the types of RNA molecules being produced and the hormones being produced. The first thing we noticed, quite unbelievable to us, they quit circling. Two weeks later

they had normal running and walking behavior. Two mice that only have one copy of the mutation, they have normal hearing, vision, behavior and these mice have 2 copies. He continues to run in circles and this mouse walks normally. You can see the foot pattern. In this box is this mutant mouse, with 2 copies of the mutation. He runs in a lot of circles. This mouse has normal walking behavior similar to a normal mouse. The next thing we did is measure their hearing. Those without the control treatment are deaf, they don't have response to sound stimulation. A mouse with only one copy, a carrier, has normal hearing and weaves in response to sound. And the other mouse treated now has nearly normal hearing. We were so excited.

And lastly we tested the vision. The mice treated in adolescence, teenage mice really, and we treated adult mice. So the red bar is to visual function of our Usher mice that have 2 copies of the mutation and they have either no treatment or the control treatment and the black bar is the mice with only one copy. You can see the size of the red bar is reduced. The blue bar are the Usher mice that received the ASO, and that particular bar is closer than the mice that received no treatment. This shows we improved the mice. So we're very, very excited about this. We are right in the middle of completing this evaluation. We're continuing to test the effects by using different doses. How long this improvement lasts and the next step is to go to Usher patients. So to just summarize, there has been significant progress with successes or promise in treatment specifically for Usher Syndrome. Doctor Pennesi is going to tell us about USH1B.

We're also investigating gene replacement therapy for USH1C. USH2A using viral and nanotechnologies. So it's a really exciting time. A lot of successes in the laboratory. Successes of these types we hope will pave the way to move more quickly than other types. So finally I want to say thank you. These are the researchers in my lab in Louisiana. To develop the ASO as well as a company in California called ISIS, unfortunately for them. It's a bad time to be, called ISIS. For the hearing side only with Gwen Gaelic as well as strategies with Luke Vandenback. I also want to thank NIH and also thank you.

MARK DUNNING: Thank you very much, Jen. There are a couple of things I forgot to mention before. We will have sign up in the lobby at lunch for the Usher Syndrome registry. And it's going to become more and more critical, as we near clinical trials, to have access to you to tell you about the trials and hopefully the treatments in the trials. If you are interested you can follow us on Twitter @Ushercoalition. We are actually Tweeting the conference right now. There's our live Tweeter over there.

Now I'd like to introduce Dennis Clegg. He's the principal investigator at the Clegg lab at the University California Santa Barbara. Give us a second because we have to switch laptops.

DR. CLEGG: Thank you very much and thank you to the organizers for the invitation. The signers are amazing. How do you sign something like docosadienoic acid? That's an amazing thing. Thank you.

I'm going to talk about stem cell therapies for eye disease. In the end, talk about the exciting work going on in the field of retinitis pigmentosa and macular degeneration.

I'm going to talk about cellular therapy. If you search images or cell therapy you get this. It's a shampoo. We're not going to talk about that. We are going to talk about what might be considered the next pillar of medicine. You have biologics that you can inject and some consider the next step is cells that you can inject or place specifically in a region. A molecule drug goes all over the body, and you have to study where it goes. All kinds of goodies that can repair tissues.

I do teach intro to biology and you guys are getting quite a lecture today. I thought I'd throw in a midterm. I don't see a pencil, but here's your exam question. What is a stem cell? I'll give you some choices. Here's your first

choice. A. The cell from a stem of a leaf; B. The latest cell phone from Apple; C. A prison cell in the show Orange is the New Black; or D. A self-renewing cell capable of differentiating into a specialized cell. What's your answer? Who said C? D is the correct answer. To be a stem cell, you have to be able to grow and reproduce and make copies of yourself; and second, you've to be able to change into a specialized cell. So you might start off as a regular cell and then change into a special cell like a rod or cone. Pluripotent cells give rise to most cells in the body and multipotent cells give rise to other cell types. Pluripotent includes embryonic cells or IPS cells, and these are cells that Jen mentioned where you can start with skin and turn it into a very powerful stem cell. Multipotent include adult stem cells or adipose fat cells, and they are not quite as powerful. They can make a few cell types like brain cells or photoreceptors. So people are studying both types for various diseases.

Where do embryonic stem cells come from? I think there's a lot of misinformation about embryonic stem cells. I have to give you a little early biology. When the sperm meets the egg, it divides and proliferates and forms a blastula. You can see what's called a blastocyst. It’s a hollow ball and there's a cell cluster on the ceiling of the ball called an inner cell mass that gives rise to the embryo. And that's where embryonic stem cells come from, from day five of a blastocyst. And there's an image of a day five blastocyst. Back in the '80s, working in mice, researchers plucked those out and found you can make any part of a mouse. And it wasn't until much later they deserved it can be done in

humans. There are blastocysts sometimes left over after in vitro fertilization procedures. Rather than throw these away, some couples have chosen to donate them to science to make stem cells. The beauty of these is when you pluck these out, as far as we can tell they go forever. One donated blastocyst can generate therapies for millions of people.

The first to grow them is Jamie Thomson. Here he is on the cover of Time Magazine in 2001. It was years before his lab discovered how to make them in humans. He was a partial appointment at UC Santa Barbara. He's helped us quite a bit. This is what these cells look like. They are different to a degree. This a colony of cells. They have to grow on a feeder layer of other cells types or specialized substances, and it's almost an art form. I found evidence it is an art form. You can say, there's Van Gogh's Starry Night. It looks a lot like stem cells.

Now what about these so-called skin cells that, that skin stem cells some call them. This was an amazing discovery in mice in Japan and later in humans. A little punch of skin can be transformed into an embryonic stem cell and they are called induced pluripotent stem cells. The embryo is turned on then reprogrammed to think it's an embryonic cell again. If you try, to my knowledge, to go in and make it into ocular cells it won't work. But you can make ocular tissue from the induced pluripotent stem cells. It has the possibility of being matched to a particular person. Make cells that can be transplanted into my body and not be rejected. It also provides the opportunity to study a disease. If we have a patient with a disease we don't understand, we can go the iPS cell in a

dish sometimes called "disease in a dish". When what you can do is take some of their skin, turn it into brain cells and ask what's wrong with these cells and maybe find drugs to correct those cells.

There are also adult stem cells. Your most abundant cell source of your body right now is adipose cells in tissues. And a lot of people are studying those as well. And the answer is it depends what you want to accomplish and really more research is needed. We are at a very early stage in stem cell research.

Why are people excited about the research? Well, there are possibilities for treatment of all kinds of diseases. You can see them here. And it's sort of, as I said, in the early '80s it was like space exploration. It involved a collaboration of many scientists.

I always like to mention the challenges we face. There's a lot of hype in the field and you can find a lot of stuff that isn't true. Say you want photoreceptors. It may be difficult to obtain a suitable population of cells. The cells may not survive. They may not integrate and function, especially in the case of advanced disease pathology. Immune rejection. It might be rejected. And finally the FDA is concerned about the cells going out of control and forming a tumor. The undifferentiated iPS cells like to grow, and that's a concern.

I'd like to mention to beware of snake oil. In foreign countries, and also in the United States, stem cell purveyors prey on patients, and you have to check with a physician or professional in the field to see its a legitimate thing.

Research in the eye may be a good place to start. There are advanced surgical methods. There are good ways to see if it's working, and good ways to image the cells to see if they are going to the right place. And we lack treatment for ocular disease. We probably all know someone affected by these various diseases.

The idea of regenerative medicine; what cells do we need? Ben showed a picture of the retina. In Usher, you need photoreceptors. In macular degeneration, the cause we think is the lack of function in the RPE. In glaucoma, it's the ganglion cells. You may want to have a combination of cells like in Stargardt's or macular degeneration. Add a support cell at the early stage of the disease and keep the cells alive, keep what you have alive. So a lot of different approaches.

How do we make the cells? Both embryonic and iPS are known to have been converted to ocular cells. In Japan, they put the stem cells of a mouse in a dish, and they noticed in the mouse embryonic stem cells, they said wow, that looks like an eyeball, they saw it developing in the dish. Human-type cells from skin and made optic vesicle type structures. All the cell types in the eye, including photoreceptors. We have been able to show you can make RPE cells. And the nice thing about these cells is that they are pigmented. You can enrich them and get a nice homogeneous generation.

Generation of RPE cells from stem cells is the work of Britney Pennington. We are funded by the Foundation Fighting Blindness. Multiple cell types and I'll

show you a number of ideas we developed with these cell types. We work with Cellular Dynamics in Wisconsin.

I want to talk about another therapy for dry AMD. RPE cells degenerate in AMD, but some viable photoreceptors remain, especially in the early stages. Research has shown that if you can restore that RPE-photoreceptor interaction you can restore vision.

There is a project called The California Project to Cure Blindness funded by the state-funded stem cell initiative called the California Institute For Regenerative Medicine. Myself and David Minton are co-investigators. We work with these various institutes. (Please refer to slide). The idea was to bring people from various walks of science to create a clinic. We got a grant in 2010 and our goal is to create a trial in 2015. Our approach was, to imagine a scaffold, go a model layer of RPE. The scaffold in this case is called Parylene, a polymer already approved for use in the eye. Here's a picture of the cells growing. They look like normal RPE cells. We have tests transplanting this into rat models and shown here is a cross section of a model of the eye of a rat. You can see the scaffold. We can see this nice placement one week after transplant. But a rat eye is very different than human, so how do we work out the surgery? The idea is to cut a slit in the side of the eye, remove the vitreous gel, make a bubble and displace the retina, cut a little hole there and insert this patch I talked about encoded with the cells. And we place them in the area where they were dying and causing the disease.

What you're seeing here is a video of a surgery. They're removing the vitreous here by suction. Now we are going to inject the fluid. And next you will see our patch set on top of the eye and we have this surgical tool that folds up like a taco and protects the cells. It's inserted in the side of the eye and then the patch is extruded in the hole in the retina. The surgeons think they can do it in one hour. And it's not too different than to fix a retinal detachment. So, looking forward, there are a lot of people going towards clinical trials with patches or RPE or stages of RPE. In our case, we submitted an application to the FDA. It was approved in March and hopefully we can start a clinical trial soon. We are already in a Phase-1 trial doing a.

There are developments all over the globe. Researchers in Israel, Japan, and London are pursuing different approaches to macular degeneration. Look at the improvements to the Saturn V rocket. I think we're at that stage. It's a very exciting time. You have heard about the various approaches and we hope some of these practices will help us. I'd like to thank the people that did the work, especially our funding from The Foundation Fighting Blindness. Thank you for your attention.

MARK DUNNING: Thank you very much. As you guys can see, there's a lot of promise in research. You're going to hear even more when Dr. Pennesi talks. Right now we have a very important task, which is to go eat. There is a buffet out there.

You can grab your food and come back here and hopefully use the opportunity to network. We'll start up again at 1:00.

MARK DUNNING: Thank you everybody. Let's see if we got everyone settled here. Thank you for coming back on time. That's always the hardest thing to stay on time. Especially running on deaf-blind time.

This afternoon, we have a couple of things. We have one more scientific presentation and then a brief change on stage and then a brief Q and A from the audience. And then a panel which is probably the most popular thing we do. But right now it's my pleasure to introduce Mark Pennesi. Mark, the floor is yours.

DR PENNESI: Thank you very much. It's really exciting to be here today and I'm really looking forward to telling you about this trial. It's really an amazing time for me. I see patients with Usher Syndrome pretty much every week. When I started in this field, maybe seven years ago, there were no clinical trials at all. But we now have a gene therapy trial and many more. Soon the trials will be coming to the clinic.

I'm going to talk a little bit about gene therapy and then about the testing patients get and many of you will probably be familiar with that. And then I'll show preliminary results of the trial. These are preliminary findings. Before I get started, I want to acknowledge my colleagues. This really represents the work of many people. (Please refer to slide).

I always like to start with a little history. The first person credited with describing Usher is Albrecht Von Graefe. Then, Charles Usher described 68 patients with retinitis pigmentosa and deafness back in 1912.

This is a typical picture of what I see when I look in the back of the eye. This is what a normal retina looks trike. In the back is the optic nerve. With a patient with Usher Syndrome, the optic nerve becomes pale. As you heard this morning, Usher Syndrome is a syndromic form of retinitis pigmentosa. Type One patients have very severe retinitis pigmentosa. Many patient get cochlear implants which may help. They also have problems with balance, for example, children find it difficult to ride a bike. Type 2 is less severe. Eye problems tend to start later in life and the deference is not as severe and most patients will have hearing aids. They tend not to have balance problems. But there can be problems with the teeth, and that is something recognized only recently. And finally one of the rare forms, Type 3, it starts as type two but the retinitis pigmentosa is more severe.

In the last ten years we've unlocked many of the genes in Usher Syndrome. In Type 1, there are 8 genes, Type 2, 3 genes, Type 3, 2 genes. One particular type today, Type 1B Usher Syndrome, is a mutation of the MYO7A gene. "A" meaning you may inherit 2 mutations. Prevalence is probably one in 100,000. This is a gene shared by the photoreceptors as well as the hair cells. These patients, like most with Type 1, have severe deafness. This is a picture of a patient with type 1B and this is looking at the back of the eye and you see black pigments and this is a sign of the retinal degeneration. If we put a special filter

here, in essence it highlights the remaining areas of the retina, and if we take a special scan you will see the retina is quite thin.

You heard this morning from Jennifer about an essential dogma of biology, which is that we all have DNA. These are proteins, and they are building blocks for cells. A disease is a mutation in a gene. You are missing a protein and the cell is going to die. In other cases, the cell may form a mutant protein. In Usher Syndrome, it is usually the first case, not enough protein made or doesn't work properly. So in this case we want to replace the missing gene.

Ultimately we want to get a normal copy of the DNA of the gene for that cell. And there are different ways to get the DNA into the cell. You can just inject bare DNA in the cell, but that is not efficient. Viruses are particles evolved over the years with the specific job of putting their DNA in cells. So we can kind of hijack them and eliminate the parts that make you sick. But some genes are too big, so there are other ways to deliver it to the cell, like with a nanoparticle. This is a schematic showing a cell, and the virus will bind to the outside of the cell. It is taken in, it releases to the nucleus and sets up shop to make a new protein.

So there's the eye. And what I want to do is put the gene therapy under the retina so it can go to the photoreceptors. The particles create a blister or fluid.

What we use is a very fine needle. This is a 41-gauge needle, so the tip of the needle is about the size of a human hair. We create a blister of fluid.

That actually is actually the easier part. The larger part is conducting an entire trial. And this is not something that happens in months. It happens over years.

Just to give you an idea of the FDA approval process, there are different phases shown here. Often, we start in the lab trying to figure out if a drug works, trying to invent something. That can take years. From then you submit it to the FDA and get the okay to do a clinical trial. These are released in different phases. The first phase is looking at safety, the second is testing, where it is definitively proven the treatment is working. This whole phrases process can take 6 to 7 years. After that, it can take seven years before they approve the treatment.

In thinking about gene therapy trial, a lot goes into how we pick patients. We have to think about whether or not we have genetic testing. We can have two confirmed mutations. We have to think about what kind of vector we're going to use. How are we going to deliver it. How much of the retina are we going to use? How do we determine successes? Do we slow down degeneration or improve vision? All of these things are important. The trial we have conducted for the past few years, this is a phase one trial. This has been a collaboration with Sanofi, a company has made the vector as well as the collaborators in Paris. This is using a specific virus, this is a virus not known to cause any disease in humans. It causes a transient anemia in horses. Why is this used? The MYO7A is too big and can't be used in gene therapy. We start off first with adults and then with patients that have severe disease, or have the definition is patients have legal blindness. We start with the low dose of the virus. It may not be an effective dose, but we are looking at safety. Finally we test at the highest dose. If everything goes well, the next step is to treat children.

How to determine if the therapy works? We test many things. The first example is pictures of the retina but more importantly, we look at the thickness of the retina, the edema of the retina, which is common in patients with Usher Syndrome. Then we segment out the layers of the retina and measure how much thickness is changing over time. This is a likeness of the retina in a normal patient and then one with the disease. Many of you have probably have had on electroretinogram. They put an electrode of the heart. An ERG is an electroretinogram, where we put a special contact lens in the eye and get signals that tell us how well the retina is functioning. This is a multifocal ERG. We show the patient a checkerboard of stimulus. You see there is a peak of the highest post receptors in the eye. You can see in the patient with Usher Syndrome how diminished this is.

Visual fields is another test we rely on very heavily. I like to tell kids this is the most boring video game you'll ever play. From that we can map out the existent of the peripheral vision. This is an example of a patient with Usher. You can see the large areas of peripheral vision lost, but there is some vision centrally.

Sometimes we change it up a little and instead of have moving targets we have flashes of light. One again, this shows a patient with Usher's. There is a large donut of area where the patient cannot see. We can plug this in and make these volumetric graphs. From the normal patient, this is the patient with Usher.

You can see a sea of red where the visual sensitivity has increased. You will see pictures from our trial in a few minutes.

Today we have now treated five patients, so we have finished the lowest dose and we have one more to treat at the middle dose. This is an example of one of the patients that was treated. This patient had 20/50 vision, which is not terrible. But they had visual fields of less than 20 degrees. What I'm now going to show you is we can take a picture of the retina and over lay the on top. Now you can see where they have remaining vision. In this patient, you can see out here in the periphery, you have vision. Over here, not so much.

So we can use this to determine gene therapy. What we want to do is try to treat at the borderline to prevent this area from degenerating. This other patient had more vision centrally and the injection was made right here. And the blood came here in the center of the eye and here, not quite. So this half of the retina has been treated this other half is untreated. Immediately after you perform the therapy, you can see there are red but after 24 hours, the retina will flatten back out.

So what happens? First, this is preliminary data. That's not surprising because we detached the retina. Over about a month, it recovers. A slight improvement in vision. This is an only a slight improvement, but we can conclude this is a safe technique. We do see a decrease in vision. Then it’s a little bit better than baseline.

One other interesting thing we noticed that in some of the patients that had swelling in the retina prior to treatment, it seems to have disappeared after treatment. This is common in patients with Usher Syndrome. Swelling or edema. Even those treatments don't work that well, and this can impact central vision. So what we noticed is one month after treatment the swelling disappeared, and in this picture, it improved about five letters. What we see is that they actually do disappear. Here is another patient where there were cysts in both eyes. This is the untreated eye, at week 12 the cyst disappeared. This is something that's very interesting.

We can also look at the visual field sensitivity over time comparing the untreated eye and the treated eye. This is shown here and one begin this is very preliminary data. The treated eye is always the worst eye after surgery, there is a drop in sensitivity over time. You see a little increase, it’s hard to say. This is a safe technique.

In conclusion, the gene therapy thus far tends to be safe and well tolerated. It's still too early if it's going to slow down degeneration. It's too early to say the change is significant over time. Two eyes diverge.

We are still recruiting for this trial, so if it's something you are interested in, please get in touch with me. These are just some of the people involved. Thank you very much.

MARK DUNNING: Thank you very much, Mark. Just a second, we're going to do a quick change of the stage and then ask our scientific presenters to come up. Give us a couple of minutes to move things around and then we'll take questions.

MARK DUNNING: Okay, we're ready to go. How about a hand for Dexter and Chris. Christy and I has a microphone over there. We have an interpreter so we are trying --

Does anybody have a question? Raise your hand. QUESTION: I have a question probably for Mark. It relates more to 1B more than 2A. You're doing a clinical trial on 1B now. If that turns out, do you have to go back and do the trial for, like, two A.

A. At this point in time, the answer is yes. The FDA considers every gene product separately. Even if all we are doing is switching out the gene, they consider that to be a new drug that requires a new clinical trial. That doesn't mean that if we had an FDA approved therapy it wouldn't be able to happen faster. The difficulty more with 2A is the size of the gene. It don't fit into the viruses we are using for 1B. So people are using different strategies for delivering it, or using some other means of delivery such as a nanoparticle. That's an obstacle that has to be surmounted for 2A.

Q. I was wondering about what you're saying about genotype and phenotyping different types of mutations that may be able to predict more specific diseases. Are there any research and trials going on in younger patients and

mutations that have bodies to offer? I know we are not participating now, but I wanted to know if there should be anything aware about because my children are so young still.

A. That's a great question. There has been a natural history study. I recently was made aware that I don't think it is still open. But that may be one to look at through clinicaltrials.gov. We in Louisiana are doing a specific study with USH1C. So we're starting with the opportunity of natural history study involving tests already run. Besides that, I'm not aware of other studies going on right now, but a good way to be contacted is to sign up on the Coalition registry. They can contact you to let you know a study is going on. You don't have to know your genetic type to sign up. You can sign up knowing you have Usher Syndrome and that's it. You can update your registry later if you decide later to get genetic testing.

Q. Something I want to get clarification on. I believe at some point even as on adult that has lost their sight, that some of these can restore their sight.

A. Yes. They have to have cells available to treat. So patients there are young and still have cells available can be a candidate for one therapy. But older patients that have lost their sight and also their cells would benefit from a different type of therapy, such as stem cell therapy that Dr. Clegg is working on. There are different studies under investigation in the research lab problem different stages of the disease.

Q. Anyone else with a question?

Q. Thank you for the work you're doing. I have a question about retinal detachment. I assume that in the surgery the reattachment occurs? I also want to ask if it lasts throughout the life of the patient. Is there concerns to do multiple retinal detachments?

A. This is something everyone has been concerned with. I think there is certainly an evolution over time, how can we do this better and better. The good news is that it didn't appear that it is as bad as, like a friend that has retinal detachment. These are very trauma from that. It is going to take long term studies to determine that. But there are situations where the patient has a detachment of the fovea with 20/20 vision, and have 20/20 vision after that. The other approach is that there's trials now, and we just started it, where we do intravitreal therapy. In certain diseases, the retina is fragile and in detachment, it will make a hole in the retina. The might be in 5 or 10 years, most therapy is done intravitreally.

I can just add about stem cells, in the model, we do see good reattachment similar to what Mark is describing.

Q. So it’s a natural reattachment?

A. Right, a natural reattachment.

Q. My question is for all the panelists. I understand you are focusing on a particular gene such as 1B, then 1C, D, E, later. But it seems unfair to patients

that have a certain type of gene to have their vision improved and then others don't. Is there a way to do all the genes simultaneously?

A. I guess maybe with more money. There are a number of reasons for why any one strategy is being investigated by a person or lab. Some has to do with science or technology. We don't have the technological advances to use gene therapy with larger genes yet. See we are moving alone with smaller genes, such as USH1B and USH1C. As much as we would like to work on all together, we have moving along.

That's the daunting question we hear a lot. Because there are more than 250 genes that can cause a retinal disease when mutated. That's a lot. And we currently fund about 120 projects. Like Jennifer said, there isn't enough money to do everything. That is where other treatment approaches. And there are gene therapies that are therapeutic but not replacing the mutated gene and those can be universally.

If we think about the first gene therapy trial, which was in a disease called. This is a gene that's very rare. Probably 350 people in the United States have it. But that trial is the first that showed gene therapy could work. And that opened the gate for other diseases. The better we get out of doing it. Just because we are not working on a specific gene that's doesn't mean we are not going to. Believe me, I want to work on every gene I can

Q. I have three questions. First question is, if a person already has had eye surgery, I've already have retinal detachment, would gene therapy be good for a person like that?

A. So when we conduct clinical trials, we're picky who is enrolled in the trial, and reason for that is we want to make sure any changes we see is due to the therapy and not the disease. So there's often exclusion criteria such as glaucoma or a retinal detachment. That might mean you would have to wait for a later phase trial, rather than be eligible for the early phase trial. But that doesn't mean it won't help you later on. As we show the treatment works, I don't think we would we would can excludes someone for the same reasons we would exclude them early on

Q. My second question, is for DHA. I had a doctor that said that someone that has Usher should take vitamin A. I'm taking 15,000 units of vitamin A. What amount is good?

A. There are a few things to keep in mind about it. The first study looked at some forms of disease and not others, and I can't remember which forms of Usher he looked at. He used 15,000 IUs in his study he always added DHA and lutein. If you go to the foundation website there's about ten pages that list all the ins and outs of vitamin A therapy. The only thing I can say is that you do it under the guidance of a doctor. Because it is a high dose. You shouldn't self-medicate.

Q. My 3rd question - is there a good place in Louisiana to do gene therapy?

A. Genetic testing? Yes, there are a number of places in Louisiana. There are a number of genetic clinics associated with both LSU and Tulane and Ochsner.

MARK DUNNING: Another question in the front here.

Q. My name is Dan and I've got 101 questions, but I'm going to condense them to just two. The first one, I understand has spent a lot of time and money over the years. I wonder if there will be a way to save time with good vision, is there possibility of transplanting eyes?

A. The question is can we transplant a whole eye and repair the tissue? That's the generally idea of stem cell therapy and it may be difficult to do a whole eye. But maybe individual cell types, like photoreceptors. You could rebuild the retina and as the technology gets better, we can rebuild the system of the entire eye.

There are researchers looking into that. It's almost science fiction-like at this point. There are researchers exploring eye transplantation. The challenge is the optic nerve has got about a million fibers and to make that connection work in a transplant is pretty darn tough.

Q. My next and final question. Somebody said about improving, once this is I wonder how I can sign up for clinical trials. Where would I go and how would I do that?

A. I think there are a couple of ways to get great sources of information. Foundation Fighting Blindness is a great source. If you want to get more into the details, get to clinicaltrials.gov, type "Usher Syndrome" and you will get all of the clinical trials under way.

Q. The first, in response to the earlier question about vitamin A, I want to report I've had vision improvement shortly after starting treatment with 15,000 units and I was on the drug for about 15 years before I got any changes in the indicators for the liver enzymes in the liver. I was tested every six months. To my question, many retina specialists discourage people with RP from getting their cataracts removed. I was wondering if, later on, in later stages of cataract development, that cataracts would make a person unsuitable either for clinical trials or for treatment with stem cell therapies or with the genetic, the other therapies there are used for RP.

A. Yeah, I think I can speak to that. The decision to take out a cataract is based on a number of factors and you always want to look at the risk versus benefit. The profile is often different than because when you take a cataract out, you are exposing the retina to a fair amount of light. You want to make sure it's done quickly because there's a potential, if the surgery goes a long time, you might have toxicity to the retina. We often tell patients with retinitis pigmentosa to wait, because taking the cataract out won't really improve the vision. So you want to minimize the risk.

After a time it may be time for the cataract to come out. To answer the second part of your question, yes, if the cataract becomes bad enough not to be able to see in the retina, we can't do surgery, we can't do the imaging or the things we need to do with a clinical trial. So are there have been times that we have had patients with surgery either who haven't had surgery. But ultimately I think the decision to take the cataract out is one made with your decision. It's not one-size-fits-all kind of decision.

Q. Just a couple of questions. With the FDA approval and the processes you have to go through with the other approvals, if we see a progression is there a chance that a European trial we be available before a trial is done here, in one of the other countries. And then second question on that is, seems like all the diseases, seems like all we have to treat the symptoms, not to treat the disease. Where does the person pop up in the radar? My daughter has Usher 1B.

A. The answer to that is yes, the goal of the registry to inform patient about clinical trials and other treatments as they come available, depending on the type of patient. If there's 1B trial, we contact 1B people, etc. I'll just say something brief. As a patient, you are a free agent to go to another country and participate in a clinical trial. In some situations they may not accept you. In France, they will only take patients in the French system. We have people coming from Switzerland to our site because France won't take them. You are free to go other places; for example, with the retinal chip implants, some have gone to Germany for that.

Q. I have a couple of questions. The first is for Dr. Lentz. My daughter has 1C. What would be the delivery method of ASO is to make it.

A. Right. Only intravitreal injection.

Q. This is for anyone, what would you start testing to test her vision?

A. I think that generally when we test young children is to assist in the diagnosis. Since you already have a diagnosis, doing an ERG where sedation may be needed, you can wait until they were a little bit older. Visual field, you have to be about 6 or 7 before a kid will behave and sometimes even that is a stretch. But one thing I think is important to look at in children is macular edema. If they can do some imaging to see if there are treatments for that. So that might be worth looking into.

Q. My name is Carly. I'm curious, I'm going to assume the mice in the study have the same routine, do you see if they are progressing at the same rate. I guess the thing always on my mind is that you can be diagnosed with 1B but everybody can progress differently. So does exercise play a role in that?

A. We have not yet begun investigating more environmental factors like diet and light. Currently all of our mice are identical with the exception they are carrying either one copy or two of the gene we're interested in. The only difference in light is that those on the top shelf might get a little more light than those on the bottom shelf. But it's a really good question. With that being said, there is a small variation with all of our animals. They are not all identical in terms of the symptoms but they are pretty close.

Q. First of all, I want to thank all of you for what you do. No way we can show our appreciation.

Secondly, I missed some parts, I don't know if anything about gene editing has been mentioned and I'm wondering, for my own benefit, if 1,2,3,or 4 might be done and what needs to be done to prove that out. I understand it's very exciting.

A. We all go, I think we all went to arval this year. That is the big ophthalmology research conference. Crisper was the hot topic. Let me back up. A lot of the gene therapies you hear about is the delivery of a whole new gene. Crisper is almost cut and paste. You're repairing the person's existing gene. Anyway, we a call it gene editing. You can get some efficacy. But there are off target effects, some parts of the genome you don't want to effect. It's still somewhat at an early stage. But it's still an exciting opportunity. We're funding somebody at Wilbur Eye institute to do Crisper research. We're just allocating funds now. Stay tuned. It's a really exciting approach.

Q. My question is about stem cell research. Is that specific to any type of Usher Syndrome?

A. Good question. I was thinking about that earlier, so many genes. One of the nice things about stem cell research, it doesn't matter what mutation it is. You can replace the photoreceptors with those from another person and you wouldn't have to correct each gene. So yeah, that's a really good point.

Q. Is there an age requirement?

A. Good question. In our case, we haven't really thought about going to younger patients or newborns. But I think it’s possible and it would perhaps be a little bit of different surgical challenge, and maybe Mark can speak to that. But it something that in the future might happen.

Operating on kids is challenging but people do it

MARK DUNNING: Any other questions out here? Hang on. I'll get you the microphone.

Q. As we talked about gene therapy and what the pharmaceutical companies, Is there anything done to make sure they are affordable?

A. I don't know if anything is being done about that. One thing to consider is that these are very rare diseases, and so I think the companies are not necessarily expecting to make money of the product. So they will probably offer it at a -- there's been talk with Sparks how much to charge. Let's say it does get approved how much to charge for it. What they charge for it and what will pay for it are two different things. Whatever the cost is, the cost will come down with technology. And if it is shown these therapies are effective and can prevent a life time of blindness, that's priceless. You can do the calculations. Legally blind times X number of years. Once we have effective therapies it will be easy to cover because they will save money in the long term

Let me add to that one of the arguments the companies make is that they put a lot of money in research so they have to recoup those costs. In California because a lot of stem cell irk is done by state grants, they can't say that.

Q. I think somebody already asked this questions but I think I could reiterate. My question was is there hope all across the board. Because there's so many different types, I think you were saying stem cell is most hopeful across the board. Has there ever been shown or been any evidence this type there is nothing you can do for this type? Cochlear implants, sometimes they work, sometimes not.

A. I don't think whether I had given up hope on, I want to cure all of the diseases and I think it's possible. It's a question of time and of money. It's not anything I've seen that suggests we can't do it. Some diseases are harder to treat than others and there are technical challenges to that. That just means we have to be smarter. You can see from the manual here there are many approaches. Sometimes there may be a combination of approaches. There's no reason why these things can't be put together to achieve what we want.

I think I would just add the short answer is no. I don't think anyone of us think there is a type that can't be treated. I think there are some types that have tools we are trying to optimize to see if they will work. In that case, we might not have tools yet, but we are researching how to build the tools.

One approach that I don't think has been discussed today is optogenetics. I bring this up in response to your question. Let's say in with us case. You lost all your rods and cones to Usher Syndrome, therefore completely blind. They are coming up with therapies that make other parts of your retina light extensive. There are other cells in the retina that survive after the photoreceptors are gone.

Researchers are making them light sensitive. Those work regardless of the gene that causes the disease and even if you have lost all photoreceptors. So that's exciting and shows there's an opportunity for everybody.

Q. I want to clarify. Can cataract surgery and gene therapy or either type of treatment or procedure (Can't hear the person.)

A. Every trial is a little different. In many trials, having cataract surgery is not necessarily a factor. In some ways its good because we have a clear view to the back of the eye.

Q. I have a question about stem cell therapy. If you replace the damaged cells with stem that but haven't corrected the gene, will the new cells get damaged?

A. That's a good question. You're still going to have the same mutation. There are two options, one would be to correct the mutation, to take the skin and make an iPS cell line, but that takes a while and is expensive. The other way is to make a bank of cells, kind of like blood typing. You would have on the shelf the iPS cell in a vial. You make that into an eye cell and put that in and you can test that and make sure it doesn't have a genetic mutation. But that is a concern.

Q. Once again, thank you all for your time and dedication to our illness or disease, however you want to describe it. Most of us know we're losing our hearing and vision. But Mark was talking about enamel. Can you elaborate more?

A. There has been some anecdotal evidence that patients with Type 2 Usher Syndrome may have enamel problems. I have seen it with a couple of my patients. A parent came up to me and said my kid has ten cavities. It's something we don't really understand.

Q. Can I ask you a question, because I had a parent contact us here and vision loss and issues with their fingernails, and they were diagnosed primarily with Heimler's syndrome. I wonder what you have heard about that.

AI never saw a patient with Heimler syndrome. Fingernails are something that can be related. Your fingernails and retina come from all similar tissues so problems with the nails can be associated with retinal dystrophy. So that can cause that.

MARK DUNNING: Other questions out here?

Q. I have a question about prevention. Jennifer alluded to the fact that here, a large percentage of people have 1CUsher Syndrome, I believe. Is there other areas of the world or states where there are lots of other types of Usher Syndrome and is that percent of the population too small to have testing to prevent Usher Syndrome

A. There are other populations and areas in the world that have a higher prevalence of Usher Syndrome. There is what we call founder mutations, mutations within a special population that results in a higher frequency of genetic disorders. They have to do with geography, religion, as well as cultural reasons, in particular a population stays in the population to find its mates. So some

special population that stays within the community to marry and have children can have the higher frequency of recessive disorders. So there is a Jewish population that is another population that has a higher expression of Usher Syndrome. Finland is another country that has a higher prevalence of Usher three because they are bound as on island. So there are other populations throughout the world that have a higher frequency of disorders. If there's a familial history of recessive disorder, the best thing to do is to go to a genetic counselor to determine your history and determine if testing is for you and how you would like to plan your family. But I would like to say every single one of us carry at least 2 or 3 mutations within our genomes. So if we found a person with the exact mutation, our children would be affected. All of us carry mutations and we all carry at least 2 or 3 that would cause a disease or syndrome in our children. Does that answer your question?

Q. Partly. I know we carry a lot of defects individual. Is it worth identifying areas in matters of prevention by tests. That's not practical because it’s such a small percent of the population.

A. I think that's a question for the individual and how they feel about planning their family. And what your position is on how you want to plan. Every individual would want to plan their family. How they would view the risk of having a child with a potential mutation.

One thing I would say is that we employ genetic counselors that can make recommendations of when genetic testing may be a reasonable thing to consider.

Q. I know Randy has a question. There was an earlier question about vitamin A and DHA supplementation. I think I can summarize it, which is what do you recommend for vitamin A and DHA for supplementation?

A. This is a very important question and what happens is, as I described this morning, we need together DHA and vitamin A going on in the back part of our eyes every day. We need both components. And both can't be made in quantity. The question often is well, how much should I take? The best published paper is by my friend who published a paper where he followed patients with retinitis pigmentosa. Treatment with both Vitamin A in a significant group of patients, he saw slowing down in the loss of sight and that is the.

AUDIENCE MEMBER: I'm having a hard time hearing you in the back

A. All right, so how are you doing back there?

So oh, my God. You want me to repeat that? The answer is both are needed. Vitamin A and DHA. And the best study is from Harvard pushed about ten years ago whereby treatments show slowing down in the side of the retinitis pigmentosa. What we're learning and that is part of what I was beginning to describe this morning, it's not just a matter of supplement, not a matter of getting a lot of it, because DHA functions a lot like vitamins. If the vitamin is in the gastrointestinal system, the liver already is not absorbed by the GI. One we found and this is something by many other laboratories. It has to go through the liver before it goes to the retina. A photoreceptor in the liver tells. So what I want to say is that the supply, there might be other genetic mobility that can impair

absorption of the fatty acid. What I told the person and what. Shown you give us a lot of hope that this knowledge would be applicable in the future. Let me tell you, ten years ago I did not have this feeling. And now we see the progress and I am thankful for foundations like the Foundation Fighting Blindness because of the knowledge. I don't know if I answered the question

Q. You did great.

A. Thank you.

Q. I've got two things. I want to say that you did a wonderful job and keep up the good work and continue the fight against Usher. We feel like we really can make it and thank you for that effort. My question, I heard in another conference in Boston, the different types of Usher, you have got 1A,B,C; 2A,B,C. Which is the most common, which is the most rare? Which of each individual type is most common and most rare?

A. The most common is USH2A and Type 2 in general is most common than Type 1. The MYO7A is most common. Type 3 Usher is quite rare. Talking about the least common, there are a couple quite rare so there's probably a tie for that.

MARK DUNNING: We have time for maybe 1 or 2 more questions.

Q. For us in Louisiana who have Type 1B,we know you're doing research on 1C, where is the closest or where should we go for treatment? Right now we went to Boston. I just want to know if we have resources closer to home

A. I think that there are a number of centers around the United States. Regionally, I'm not familiar with Louisiana. I know there's a good center in Dallas. At Baylor, there's good people. The chairman at Baylor was. Those are probably the two closest.

Q. Then if we go to Dallas, can we go through Jennifer or do we have to travel to Fort Worth or Washington?

A. You certainly can contact me and I can help you find a fashion that makes the most sense to you. But if you would have to travel outside of Louisiana to see someone who specializes in 1B or if you could work with your specialist here in Louisiana with someone in another state we can look at that

This is a question we get a lot. A good way to address that is to connect you with the difficulty specialists.

Q. I have a question. My partner decided to take a dietary supplement. It’s a shake, meal replacement and noticed that her eyes starter to deteriorate. I spoke with a friend and learned that patients are not encouraged to take Vitamin E or K and that supplement has a high volume of those supplements. My question is about vitamins E and K. Are they dangerous? I think this is something we need to be aware of.

A. I'm not aware that vitamin K is bad for Ushers or retinitis pigmentosa. Looking at vitamin E suggested that maybe E wasn't good for retinitis pigmentosa. Most of us don't really believe that as a result. We may say avoid taking successive amounts of vitamin E or K for other reasons. But I think getting a normal amount in your diet is not unusually going to cause problems.

Doctor Pennesi is on the money there. Studies show excessive amounts of vitamin E might cause problems with liver function. The same problem can be with vitamin A. Vitamin E protects us from stress. I think the answer, ask this is the right one for those two vitamins, the concentration of the vitamins should be very low.

MARK DUNNING: We have time for one last question.

Q. I think this is more for Mark, but the rest too. This has to do with outcome measurements. I know OCT is the standard used a lot for testing. I know you use Hill Vision. I also know Foundation Fighting Blindness. Between the two, will it be consistent across different clinical trials so they will be comparable?

A. Yeah, so I think when we look at clinical trials, there are two types of measurements we do. There are structural measurements, autofluorescence, OCT and the structure of the retina, then functional tests like visual fields and the function of the retina. Looking at the ellipsoid zone is a subcategory of that seems to work. It’s a fairly easy measurement to do, so it's attractive. It can be standardized across centers. The big question is whether the FDA will accept it. Visual fields can also be standardized across centers. You need a certain kind of

machine, but centers have that. Measure and I think they go hand in hand. There is a reason we get multiple tests and that's because we want to see them correlate together. Changes we see are meaningful. And the more accordance we can show, then if we see a change, it's real and not a fluctuation. The Hill vision is just a way of fitting the visual fields to create that three dimensional plot and look at the volume of that.

MARK DUNNING: Thank you all very, very much for taking the time today. We are going to take a break and get together at 3:15. As good as the program is so far, it should get even better with the family panel.