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## Curing Blindness: How Researchers are Utilizing Gene Therapy

Narrator:

Welcome to Medical Breakthroughs from Penn Medicine, advancing medicine through precision diagnostics and novel therapies. You're listening to Reach MD, and I am your host, Dr. Shira Johnson, and with me today is Dr. Jean Bennett, Professor of Ophthalmology and Cell and Developmental Biology at the University of Pennsylvania and researcher at the Children's Hospital of Philadelphia. Today we will be discussing Dr. Bennett's innovative work and research in curing blindness.

Dr. Johnson:

Dr. Bennett, welcome to the program.

Dr. Bennett:

Thank you very much. It's a pleasure to be here.

Dr. Johnson:

We have many physicians listening to this show from many specialties, but what we have in common is most of us don't work with blindness on a daily basis. Can you tell us something about the different forms of blindness and how many people are affected?

Dr. Bennett:

Sure. It's actually an enormous problem. Worldwide there are about 39 million people who are in total blindness and another 246 million have very low vision, so they're severely visually impaired. This is, of course, a burden to the individual in terms of their mobility, their job opportunities, isolation, and to their families, the people who are taking care of them, and to the healthcare system in terms of direct medical costs, and then to society, because this accounts for a huge amount of disability, work loss, premature mortality, and other problems.

Dr. Johnson:

And what are the different types of blindness?

Dr. Bennett:

The most frequent forms of visual impairment are caused by problems that can be corrected. So, for example, refractive errors or cataracts, and in the U.S., of course, that's generally not a huge problem, but in third-world countries, that is a huge problem; but, there are other forms of blindness which are a severe problem in the U.S. and other countries, and those include diabetes, which is the leading cause of blindness in adults who are over age 20, and that accounts for blindness in more than 4 million Americans and the number is rising. It may be due to increased blood sugar levels and consumption of the wrong foods, etc. So, diabetes, then age-related macular degeneration is also a leading cause of blindness. In fact, there are more than 2 million people blind in the U.S. due to this condition and an additional 14 million are at risk. This is, of course, a disease of older individuals. There's glaucoma, which affects about 1.9% of the U.S. population age 40 and above, and then there is a whole set of conditions called retinal degeneration. This includes retinitis pigmentosa, which there are about 100,000 cases, as well as different forms of macular degeneration. These conditions lead to complete blindness, and so far, we have no approved treatments for them.

Dr. Johnson:

So, what are you and your team at Penn Scheie Eye Institute doing to combat blindness?

Dr. Bennett:

It's a many-faceted approach, starting with the clinical service, of course, keeping eyes healthy when they are healthy and bringing the latest treatments, including off-site screenings and doing what we can to prevent vision loss, and then we are working very hard to develop treatments for those diseases for which there are none. That includes a number of areas of translational research, and in our Center for Advanced Retinal and Ocular Therapeutics at Scheie – this is also abbreviated CAROT – we're trying to develop biologic and small molecule therapeutics for these diseases, and when we have promising proof of concept in the laboratory through cell models or animal models, we develop clinical trials, and the clinical trials – we've already run several clinical trials for modalities that have been developed in

our own laboratory and we're also developing clinical trials in conjunction with Biotech and larger pharmaceutical companies to tackle these unmet needs.

Dr. Johnson:

Your research in the field of gene therapy has received a lot of attention. Can you tell us something about your work?

Dr. Bennett:

Sure. Well, this was a dream some 35 years ago when it became apparent that it was possible to actually harness recombinant DNA and put DNA into cells of – at that point it was animal models – and see a change based on the gene that was actually delivered to these cells. So, of course, the natural thought was, “Wow, wouldn't it be great to be able to harness this to be able to cure diseases?”—diseases where a lack of function of a specific gene causes the pathology – causes cells to degenerate and malfunction. In fact, I was in medical school with my husband, Albert McGuire, in the mid-1980s, and reports were coming out about the promise of recombinant DNA, and Al looked at me and said, “Well gee, how about we treat retinitis pigmentosa with gene therapy,” and he knew that I knew a bit about gene therapy at that point, and I said, “Oh sure,” but what I didn't tell him was we didn't have any of the tools at that point in time, any of the reagents, any of the surgical techniques for delivering the genes to the target cells in the eye, any of the animal models, or any of the outcome measures that would be necessary to show that our intervention actually made a difference and further, at that point in time, we didn't know any of the genes which caused any of these diseases. So, in the intervening time, this is several decades now, all of that stuff has come together. We now know more than 260 different genes which, when mutated, can cause different forms of blinding disease. We have multiple animal models in various different species going from zebra fish, to mice, to rats, to dogs, to cats, and even to pigs, and we know how to deliver genes to the cells in the retina. We know how to get the cells to take them up using what we call vectors, and these are often recombinant viruses which have been neutered so that essentially what you have is an empty shell delivering the appropriate piece of DNA. We know how to measure the outcomes in terms of both sophisticated imaging and also retinal and visual function testing. So, a lot has come into play, which has allowed us and other groups to be able to test gene therapy in some of the most severe forms of inherited blinding disease. That's something which has been amazing for me to witness – to be able to see this all move from a point where we had no reagents to being able to test the approach first in a dog model – this is a dog that was born spontaneously blind – and to be able to have the dog see after this intervention and then to go from there to be able to test this same approach in children who are born blind and then to be able to have them see is just astounding and very exciting and hopefully will set a path to develop treatments for other forms of blinding disease.

Dr. Johnson:

If you're just tuning in, you're listening to Medical Breakthroughs from Penn Medicine on Reach MD. I'm your host, Dr. Shira Johnson, and with me today is Dr. Jean Bennett, and we are discussing her work and research in curing blindness. So, Dr. Bennett, what does this mean for children with choroid edema and other rare genetic diseases of the eye?

Dr. Bennett:

Well, what we hope that it will mean is that these children and their families now have hope. It was not long ago – in fact, just a few years ago – that we would hear stories over and over again of families who would have a baby and it was clear the baby was visually impaired or young children who were diagnosed with diseases which progressed relentlessly and cause people to become totally blind, and those people were told, "I'm sorry, there's nothing we can do; you're going to have to take your child home and have the child learn how to use a cane and learn Brail and learn how to use a guide dog." Now, there is definitely something we can do and it starts first with getting genetic testing and characterizing the disease so that we know which genes to focus on and to be able to run testing in a laboratory to try to develop a treatment – a rational treatment – which addresses the root cause of the disease in these children, and then to develop a rational treatment addressing the condition. So now, there is a great deal of hope. There is something we can do. There's a path that has been built to be able to develop treatments for the gene defects which have so far not been addressed in the laboratory, and certainly for particular diseases, we are on the verge of having the first approved gene therapy. My prediction is that in 2017 this will receive approval by the U.S. Food and Drug Administration, providing the first approved treatment for these diseases, which heretofore have not been treatable.

Dr. Johnson:

So, can you share with us some of the long-term outcomes you hope to achieve and maybe the implications for other forms of blindness?

Dr. Bennett:

One of the biggest steps is going to be to have the first gene therapy approved for a blinding condition. This will actually likely be the first approved gene therapy period in the United States - this one that I mentioned for congenital blindness. This will help establish the path for developing other treatments. There will be a lot of work to do after that, but once we have this path developed, at least there will be a series of steps to follow. The mission after that will be to develop safe and effective treatments for as many of these hundreds of different forms of blindness as we can tackle. That will begin with the step of identifying the genes and mutations that cause these diseases to identify the specific gene defects in the various people who come to the clinics. There are now multiple labs around the country and

around the world which do genetic testing for these various conditions, knowing that treatments are on the brink of being discovered, then we will need to solve some technical challenges for some of these different diseases. For example, some of the diseases are due to mutations in genes which, so far, are too large to fit within the cargo capacity of the current vectors – the current reagents – which are used to deliver the genes, and so there will have to be some technical improvements to be able to deliver those large cargo genes. Finally, we will need to train others to carry the torch and deal with many of these different forms of inherited blindness, so continue to train young scientists and young clinicians who will carry this on.

Dr. Johnson:

So, what role does the Scheie Eye Institute play in fostering this research and bringing these treatment advances to patients?

Dr. Bennett:

Well, first and foremost Scheie Eye Institute has expert clinical care. We have amazing, dedicated physicians, clinical staff, administration, and support staff, so that's a huge deal, and it certainly draws a large patient population to come visit, not only from local areas but from around the world. This institute provides the support to nourish the dreams and goals which, right now, seem daring and bold and unconventional, such as the development of gene therapy and other modalities which could potentially be used to treat blinding disease such as transplantation of cells, development of stem cells which could be transplanted, developing bionic eyes, for example, devices which can be implanted in totally blind eyes allowing the person to see and so-called optogenetic therapy, which is an approach where cells that are remaining in the retina after the cells which initiate vision have died off are then rendered light sensitive and are able to convey vision to the brain. Other aspects about Scheie which are unique are that it provides seed funding and moral support to move forward with these goals under the inspiration of our fearless, dynamic leader, Dr. Joan O'Brien who, herself, is leading efforts to tackle diseases as diverse as glaucoma and eye tumors, and the institute has a great record at recruiting people with the same mission. Many eye doctors out there just want to go out to private practice and make a lot of money, which is something that you generally don't do in academic medicine in developing a new treatment. So, she and the other people who are recruiting individuals at Scheie have a common dream of being able to devote their lives to bringing vision to people who don't have it, and, of course, the development of all of these new approaches to restore vision or to prevent vision loss requires a tremendous amount of complimentary expertise and the ability of people with this complimentary expertise to work well together. So, this is a really unique institution, I believe, and it has really allowed people like me to be able to see something which rarely happens in medicine – to be able to see studies move from the laboratory bench to the clinic.

Dr. Johnson:

And on a personal note, could you share with us some gratifying moments where you got to experience the results of your research and tell us one or two short stories maybe of what you've seen and what it meant to you?

Dr. Bennett:

Absolutely! In the early 2000s, in fact, in 2000, we carried out our first study on dogs – these are actually puppies born blind. They couldn't move away from their crate because they couldn't see. They were scared of bumping into things because they couldn't see, and they didn't want to get hurt obviously. We took the step of injecting one eye of each of these puppies with a gene therapy reagent and within two weeks their behavior changed; they were running around, catching objects that were thrown to them; playing with balls; finding their food with no problem; finding their water bowl with no problem; totally visual. The dream at that point was, "Wow, this is amazing – seeing blind dogs now able to see!" Wouldn't it be amazing to do the same thing with children who are born blind? I've been so fortunate, as has my team, to be able to witness that many, many times and, of course, the first time that I saw a child who came into the clinic using a blind cane, holding his parents' hand because he couldn't see, and then being able to see this child walk confidently and quickly and accurately, avoiding obstacles, being totally independent, describing things that he had only dreamed of such as seeing stars at night or fireflies – this was just miraculous to me, and I thank my stars every day for the fortune of being able to witness this. I am reminded everyday too because we've adopted some of the research dogs who we first treated and have enjoyed being with them at home watching them run around the back yard, totally different from when first met them behavior wise.

Dr. Johnson:

Dr. Bennett, is there any lasting thoughts you'd like to leave us with today?

Dr. Bennett:

Yes indeed! I'd like to emphasize the point that all of the work that I've described to you is the result of having an enormously talented and complimentary team of researchers and this includes people who are experts in cell biology and molecular biology, physiology, and virology. It includes the clinicians, especially Albert McGuire, who was the brave one who took the step of being the first to inject this material into a young child. It includes the funding sources, including the NIH and Spark Therapeutics that funded the trial I told you about with congenital blindness, and it includes an incredible array of talented and energetic staff, including Junwei Sun, who is our chief administrator here at our center, and especially Dr. Joan O'Brien, who is our fearless leader at Scheie Eye Institute and inspires all of us every day.

Dr. Johnson:

Ah, those are some beautiful stories and some special moments. Dr. Bennett, thank you so much for being with us today and sharing your research and your own personal experiences with these projects.

Dr. Bennett:

Thank you so much. It has been a pleasure.

Dr. Johnson:

I'm your host, Dr. Shira Johnson. Thank you for listening.

Narrator:

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