USHER 1F COLLABORATIVE

Newsletter

Fall - Winter 2017

MY TOOLS

By Tzila Chana Seewald-Russell

When I was born, my father thought I was perfect. My mother knew that something was wrong, but she couldn't put her finger on it. This was in 1986, and newborn testing was sparse, often far off the mark, and many conditions went undiagnosed. Taking me from doctor to doctor didn't help; no one could figure out what it was that so concerned my mother.

In fact, when she took me to an audiologist (who should have been the perfect candidate to recognize my symptoms), he placed me in front of a video of a monkey clapping its hands. When I responded to the visual cue by clapping my hands as well, he ruled out the possibility of deafness, attributing my response to the clapping sounds I'd heard!

After that year, it was indeed confirmed that I was completely deaf. My parents didn't know anyone who was deaf, and they believed that in order for me to survive I needed to hear. It didn't take long for them to find out about cochlear implants-what was at the time a newish, yet past the experimental stage, medical procedure. At the age of just three-years-old, I was New York University Hospital's 13th patient to undergo a cochlear implant.

After my first implant, I could hear, but my verbal and auditory skills were virtually non-existent. Intense speech therapy several times a week helped me advance tremendously, and I painstakingly built up my vocabulary.

When it was time for me to go to school, my parents insisted that I be mainstreamed, so that I'd grow up 'normal' in a world of hearing people. Thanks to the regulations of the NY Board of Education, and to my parents' strong advocacy skills, I always had a shadow at my side.

At the age of 17, I was dealt a really crushing blow that made me forget about 'discrimination' against my deafness. Like most of my friends, I wanted the independence of driving my own vehicle. There was no reason I couldn't drive, I thought. Trouble started during a driving lesson when I was backing out of a driveway.

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"Didn't you see that car?" my instructor shouted, slamming on the brake to avert a collision.

"I didn't!" I said, and promptly forgot about it.

Several days later, I was out with my father and, as we passed the recycling bin at the curb, I knocked into a few empty soda cans which were on the ground.

"What did you do that for?" my father asked.

"What?"

"Didn't you see those cans?"

I hadn't.

In the final test, my father held out his hand and said, "This is for you."
"What?"

I didn't see anything.

"Here! Here!" he almost shouted.

"Where?"

"Don't you want 50 bucks?" he waved a bill in front of my nose.

I was a teenager; of course I could use 50 dollars. I simply hadn't seen it.

"It may be Usher Syndrome," the doctor suggested, after listening to our stories and completing an eye exam. "This means that you can see, but you don't have peripheral vision. I'd advise you to check it out with a specialist" How can this be? I already have one disability! Why are You giving me another challenge? I questioned G-d. Why? Why are you throwing things at me like this? Enough! I was angry and inconsolable! I had worked so hard to build a solid life for myself despite being challenged with deafness. Why was I now being challenged with blindness as well?

As soon as we got home I locked myself into the bathroom to wallow in despair.

"Don't do that!" my mother followed me. "Don't let this stop you! You can continue! You will! You can do anything, Tzila!"

It took some time, but eventually my mother's repetitive encouragement penetrated. By the time we confirmed the diagnosis with the specialist, I'd convinced myself that I'd have the absolutely least degenerative form of Usher's possible (which means only a slight change every ten years or so). And I decided to focus on the here and now-not on the murky future.

Later, when I was in college, I joined the Helen Keller Foundation, where I learned how to use a walking stick and how to type on the computer without looking at the keys. Though I was hopeful that I'd never have to use these skills, I wanted to be proactive.

I don't like using the walking stick. Unlike the cochlear implant, it's quite noticeable-and the first thing people see when looking at me. I almost feel like it obscures the real me by pronouncing that first and foremost, I'm blind. However, when I do use it, it has its advantages. If I step on someone's toes in Manhattan foot traffic, I'm bound to get yelled at or worse. If my walking stick mistakenly strikes someone, I'm more likely to be awarded with an apology! The stick also clears lines at ticket booths and supermarkets. After all, who won't allow a 'pitiful' blind person ahead of them?

When I became a mother, I was nervous about how I'd hear my baby during the night (since I remove the cochlear implant before I go to sleep). At first, I tried a vibrating machine which shook my mattress when the baby cried. However, my husband didn't like the way it vibrated so violently, and he offered to wake me when the baby cried. Other than that, I pretty much function like every other mother and wife.

During the day, I usually wear my implants so I can hear my kids. However, when I don't, they know exactly how to pull my hand or tug my skirt to get what they want.

I received my Masters of Social Work from Hunter College and now work as a Recovery Specialist for the mentally ill. Indeed, my clients often tell me that although I don't speak as perfectly as most social workers they've worked with, they understand me better than anyone else. Why? Because I have a way of understanding them, due to my own life experience. And if I can understand them, we can connect.

On one occasion, when I asked a new client to face me when speaking to me so that I could lip read, she burst out: "Oh! I'm so sorry! I had no idea you were deaf. I feel so bad for you!"

You feel bad for me? I wanted to tell her. Why? You are dealing with a severe mental illness that impacts your daily functioning! Why do you feel bad for me? I lead such a successful life! I'm happily married with two children. I have a job that I love. I have wonderful parents and friends! Why would you feel bad for me!?!

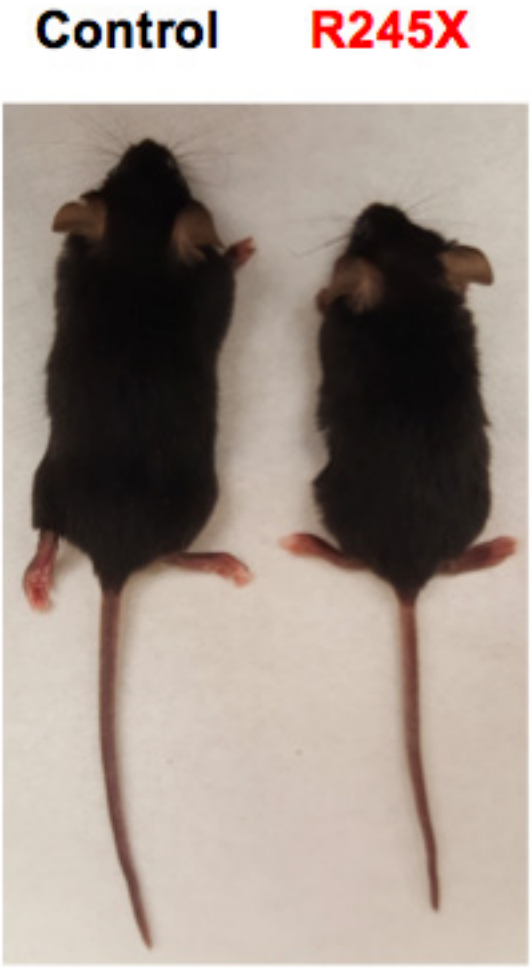
Then, I realized that the tools G-d gave me are the ones I need to deal with my personal life challenges. I wouldn't be able to survive without the resources He gave me. But, my client wouldn't be able to deal with my challenges; G-d gave her the tools to deal with her own personal circumstances. I know that I can make it work.

PCDH15 R245X MICE HAVE HEARING LOSS, BALANCE PROBLEM AND PROGRESSIVE VISION LOSS, RECAPITULATING HUMAN USH1 PHENOTYPE

By Zubair Ahmed, Ph.D.

Zubair Ahmed, Ph.D., has been researching Usher 1F for many years. He was a post doctoral student and part of the team at the NIH that, in 2002, discovered the most common genetic mutation that causes Usher 1F. After several attempts, he has now succeeded where several others have failed in creating a mouse model of this mutation that provides us with a major breakthrough in testing potential treatments and therapies for the vision loss of Usher 1F. He describes his work for us.

Through genome manipulation, we have generated a Pcdh15 R245X mouse strain (Fig. 1). Cataloguing of the natural history of vision, hearing, balance loss, and associated pathophysiology in Pcdh15 R245X mice is vital to determine the success of any future intervention strategies in patients affected with USH1F. Our current data suggest that the Pcdh15 mutant mice are profoundly deaf by birth, and have serious vestibular dysfunction as they cannot swim properly and have a strong stereotypic circling behaviour. At the cellular level, we have determined that the sensory hair cells of the cochlea and the vestibular system are not functional and degenerate rapidly after birth (Fig. 2). The mice also progressively lose vision, which means that we finally have a mouse model in our hand to understand the role of Pcdh15 in the maintenance of vision in USH1F (Fig. 3), and to evaluate therapeutic strategies. In collaboration with Dr. Livia Carvalho (Lions Eye Institute, Perth, Australia), and Dr. Luk Vandenberghe (Harvard Medical School, and Massachusetts Eye and Ear, Boston, USA), we are developing gene therapy strategies to replace the impaired Pcdh15 gene and also testing different compounds to reverse the hearing, balance and vision impairment in this R245X mouse model. Funding from the Usher 1F Collaborative has been instrumental in developing and characterizing the R245X mouse model.



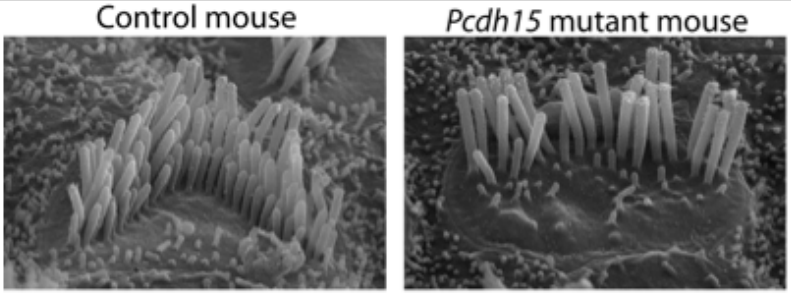


Fig. 2: Scanning electron microscopy images showing the sensory hair cells of control and *Pcdh15* R245X inner ear. The sensory hair cells in R245X mice progressively degenerate and cause deafness.

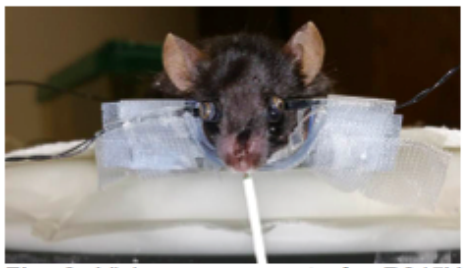


Fig. 3: Vision assessment of a R245X mouse by measuring the electrical responses of the retina after light stimulation.

OUR YEAR IN REVIEW

During 2017, we doubled our number of funded research labs, adding two new researchers, Zubair Ahmed, Ph.D., at the University of Maryland, and Livia Carvalho, Ph.D., at the University of Western Australia. Drs. Ahmed and Carvalho join our other funded researchers, Monte Westerfield, Ph.D., University of Oregon Institute of Neuroscience, and Edwin Stone, M.D., Ph.D., Wynn Institute for Vision Research at the University of Iowa. Both of our new researchers have written about their Usher 1F research for this newsletter.

With our four research labs working on a cure for the vision loss of Usher 1F, we are now funding several projects:

Gene replacement therapy - Many have asked if the Spark Therapeutics gene therapy, which received much coverage in the news recently when an FDA panel unanimously recommended it for approval, is applicable to Usher 1F. The answer is yes and no. We are working on gene replacement for Usher 1F, but we have to develop a delivery method that will work for the large Usher 1F gene so that we can realize the same success as Spark. We currently have three research projects to address this:

1. Split our large Usher 1F gene into two pieces, delivering both and then having the pieces reassemble in the eye.
2. Abbreviate our gene so that it will fit on the current virus vectors, keeping the pieces essential for vision.
3. Develop a new virus vector that will hold our entire gene.

Drug therapies - Using our mouse and fish models, test several compounds that will cause the genetic mutation that causes Usher 1F to be ignored.

Stem cell therapy – Create new retinal photoreceptors using stem cells made from patients' own skin cells. This therapy holds the potential to reverse degeneration that has already occurred.

On the horizon for 2018 will be research to see if a groundbreaking gene editing technique developed by David Liu, Ph.D., of Harvard, will be applicable to Usher 1F. Dr. Liu describes this technology as similar to taking a pencil eraser and erasing the mutation and writing in the correct genetic sequence. Jennifer Phillips, Ph.D., in Dr. Westerfield's lab has already told us that they have ordered the reagents and are excited to begin testing the applicability of Dr. Liu's work for Usher 1F.

Our board and Usher 1F Collaborative families continue to work hard to raise funds to ensure that our critical and exciting work continues. During 2017, nine fundraising events brought in a total of almost $150,000, and we still have one more to go. These events have included smaller efforts of generous families asking for donations instead of birthday presents, bar and bat mitzvah projects, bake sales, race sponsorships, a game based on The Bachelor TV show, a children's music recital, a golf tournament, and, finally Sight.Sound.Cycle, which is profiled in this newsletter. We welcome any effort, large or small, to help us in our race against time to find a cure to save the vision of those with Usher 1F.

SIGHT.SOUND.CYCLE

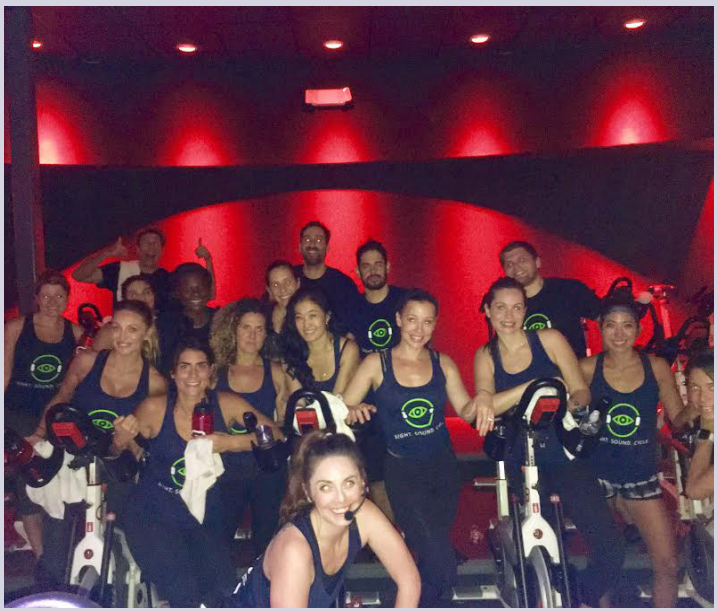
This fall, 400 riders in 13 spin studios around the United States cycled for a cure for Usher 1F. Spearheaded by Jared Root, father to Zachary who has Usher 1F, and his two friends and Usher 1F Collaborative board members Josh Herz and Matt Shulman, the event brought in a record breaking $134,000, including sponsorships of over $50,000. We topped last year's total raised by almost $50,000. Pearl Media donated their time and expertise to create a wonderful video to introduce the event at each studio. We are so grateful to all the participants and sponsors! We will see you again in the fall of 2018! If you would like to host a Sight.Sound.Cycle event in your city, please contact Jared Root at jroot@usher1f.org.

Please visit the home page of our website, http://usher1f.org, or https://vimeo.com/235177491 to watch our video.

Westchester, NY

Deerfield, IL

Long Island, NY



Culver City, CA

Deerfield, IL

Florham Park, NJ

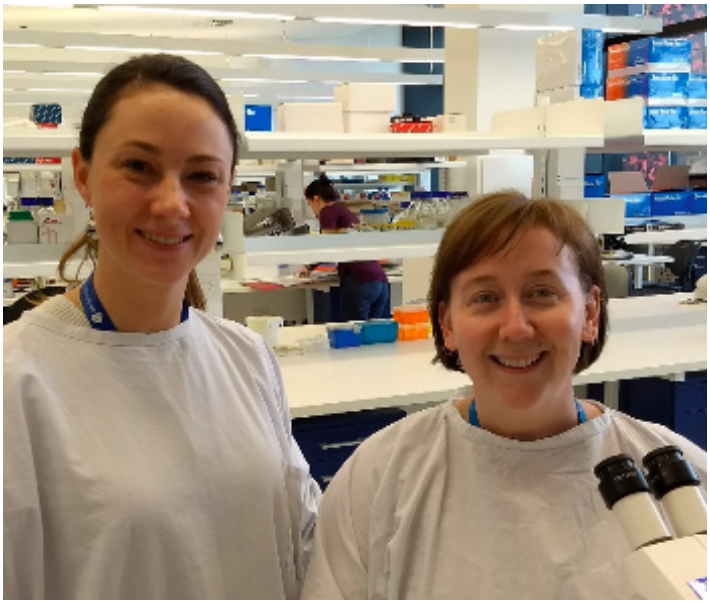
Boston, MA

DOWN UNDER USHER 1F UPDATES

By Livia Carvalho, Ph.D.

The road towards testing gene therapy treatment strategies for Usher 1F has recently been joined by a new collaborative effort between research labs in the US and Australia. The labs of Dr. Livia Carvalho (Lions Eye Institute, Perth, Australia), Prof. Zubair Ahmed (University of Maryland, Baltimore, USA) and Dr. Luk Vandenberghe (Harvard Medical School and Massachusetts Eye and Ear, Boston, USA) are working together on an exciting gene therapy strategy to deliver a good copy of the PCDH15 gene to photoreceptor cells in the retina. The strategy consists of splitting the PCDH15 gene in two halves since it is too large to fit into the virus that will deliver the gene to the cells in the retina. The two halves will be delivered in separate virus particles but will come together inside the cell to make the full length gene. Dr. Carvalho has been working on creating the two gene halves, which Dr Vandenberghe will package into the virus particles. Using an Ush1F mouse model being developed in the lab of Prof. Ahmed, they will then test the treatment therapy to hopefully restore vision in the mouse model.

Funding from the Usher 1F Collaborative has been instrumental in moving these efforts forward and bringing this collaboration together. All researchers involved are very excited to be part of this wonderful community and hope to help advance the scientific developments towards finding a cure for Usher 1F.



Dr. Livia Carvalho (left) and Dr. Paula Fuller-Carter (right) in the lab at the Lions Eye Institute, Perth, Australia. Dr. Fuller-Carter is a researcher currently funded by Usher 1F Collaborative to develop gene therapy strategies for restoring vision in Usher 1F.

Dorie Shapiro (second from right) with her brother, David Shapiro (first from left), her mother, Laurie Shapiro (second from left), and Elizabeth Shapiro (first from right).

TOUCHDOWN FOR SIGHT

Dorie Shapiro has Usher 1F, and her family is working to help find a cure. Please join the Shapiro family for the second annual Touchdown for Sight on December 17, 2017, beginning at 11 AM. The event will be held at Temple Bar in North Scottsdale, AZ, in conjunction with the telecast of the Arizona Cardinals – Washington Redskins game. Temple Bar will donate a percentage of their proceeds during that time. There will also be a silent auction and 50-50 raffle.

SEND DONATIONS

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www.Usher1F.org/Donate