



USHER 1F
COLLABORATIVE

NEWSLETTER
Fall 2021



Alex Anders

Missing Pieces

By Alex Anders

I am introduced to wearing a cochlear implant. I throw it out the car window where it gets stuck on a cactus. I am two years old.

I go to a school for the deaf, learn sign language and then how to speak. I make my first best friend. I am four years old.

I have to be in school fifteen minutes early, and leave an hour late because I attend speech therapy. I am eight years old.

I am at science camp, and I cannot touch the plasma ball because it might damage my cochlear implant. I watch all my other classmates touch it. I am ten years old.

I am at the pool, with my implant off, deaf. My friends play around me. I can't hear their voices. I am twelve years old.

I go to the beach, and instead of getting in the water, spend time on the sand with my implant on. There is a noise I'm only now aware of, a bubbling roar and murmur. I am fourteen years old.

I'm walking with my friends, and someone shouts. A skateboarder tumbles into me. My friends ask why I didn't move out of the way. I didn't hear where he was. I am sixteen years old.

"Are you sure you'll be okay to go to college? The classrooms will be big," my mother says. "Yeah, I'll just make sure to sit in the front so I can hear," I reply. I am eighteen years old.

I wake up sick, congested in the nose, with pressure behind my eyes. I see concentric rings of TV static in my far periphery. They seem like they were always there, hidden in plain sight. I chalk it up to being sick. I am nineteen years old.

I am no longer sick, but I still see the radial fuzziness. I schedule an appointment with an optometrist, because I need my prescription updated as well. I mention the fuzziness, and she gives me a black spoon to hold over my eye. She stands some distance away and holds up her arm. "How many fingers am I holding up?" she asks. I can't see her hand at all.

I am referred to another building, where they take many images of my eye, and make me gaze at lasers and bright green flashes. They test my peripheral vision, and there's a circle just outside the center of my vision, gone. "It looks like Usher's syndrome," the doctor says.

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Update on Our Research for a Cure

Since our founding in December 2013, our gifted and dedicated research scientists have worked in their labs to advance research for a cure for the vision loss of Usher 1F. We asked some of them to provide our readers with update on their progress.

Note:

PCDH15 - the gene in which mutations cause Usher 1F
R245X - the most common Usher 1F mutation
AAV (Adeno-associated virus) vector - the means of transporting genes into cells

University of Oregon Institute of Neuroscience Monty Westerfield, PhD, and Jennifer Phillips, PhD



*Drs. Monte Westerfield and Jennifer Phillips with tanks of Usher 1F zebrafish
Photo credit: University of Oregon*

We are continuing to work with the USH1F fish models to understand how the loss of PCDH15 affects visual function and retinal cell health. Also, in collaboration with Dr. Jack Arbiser at Emory University, we are assessing the effect of a drug that

has the potential to slow the rate of retinal cell death, using a variety of molecular tools and behavioral tests to compare treated and untreated groups of fish. Finally, we are using gene editing tools to see whether modifying the protein code to skip over the R245X mutation in PCDH15 improves the vision problems in our fish models.

David Corey, PhD Harvard Medical School

Usher syndrome 1F is characterized by profound congenital deafness and slowly progressing vision loss, suggesting that the functional demands on PCDH15 in hair cells of the inner ear are greater than in photoreceptors of the eye. Therapeutic interventions that rescue hearing and balance in animal models

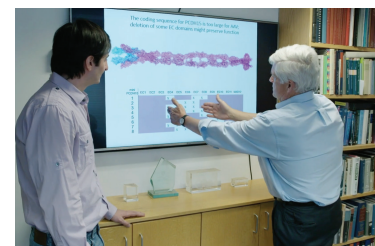
are thus likely to help vision as well. Gene addition to the cochlea or retina is an attractive strategy. However, the PCDH15 coding sequence, at 5.8 kb, is too large for a single AAV vector.

The Corey laboratory is developing methods for delivering a functional PCDH15 coding sequence to the inner ear in mouse models of Usher 1F, with the expectation that—if successful—these could treat vision loss as well.

In one, we split the coding sequence of mouse PCDH15 into two parts and put each part in a separate AAV vector. Once in a cell, AAV genomes can recombine to create a full-length coding sequence. To evaluate function in the inner ear *in vivo*, *Pcdh15* conditional knockout mouse cochleas were injected with dual AAVs. Hearing tests and histological analyses were performed at P30. We found that the AAV-delivered PCDH15 was made by hair cells and transported to its normal location. While uninjected *Pcdh15* conditional knockout mice were deaf and had degenerated hair bundles, mice treated with dual AAVs encoding PCDH15 demonstrated good hearing rescue at low and middle frequencies, and their bundles had a normal shape.

In another, we engineered the coding sequence of PCDH15 to remove nonessential domains, creating “mini-PCDH15s.” We shortened the extracellular part of the protein by about half but retained the essential domains at each end that bind to other proteins. The coding sequence could then fit in one AAV. Treatment of conditional knockout mice with AAVs encoding mini-PCDH15 also rescued the hearing and preserved the shape of the hair bundles.

Both strategies are promising for treatment of developing blindness in Usher 1F patients.



David Corey and Artur Indzhukulian studying the Usher 1F gene

Zubair Ahmed, PhD

University of Maryland School of Medicine



Me. Sehar Riaz (graduate student) and Samuel Garmoe (Research Assistant), Zubair Ahmed lab, are injecting viral vector constructs into mouse retina

Our USH1F team, in collaboration with investigators at National Institutes of Health, completed a longitudinal phenotyping in thirteen USH1F individuals that revealed progressive retinal degeneration,

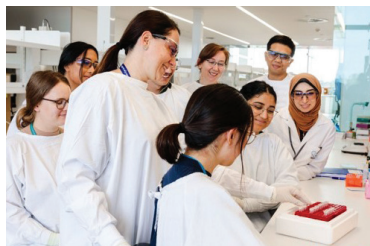
leading to severe vision loss by the sixth decade. Around half of the studied affected individuals were legally blind by their mid-fifties. Our team also developed an USH1F mouse model and found that, similar to humans, mutant mice also had visual deficits. We are using these mice for preclinical studies for various therapeutic strategies. One of these strategies was to administer to the mice a synthetic compound that is essential for retinal functions. Intriguingly, we found much improved visual function after delivery of the synthetic compound. Taking a step forward, our research team is working on the synthesis of the compound for human consumption in order to do a clinical trial to preserve vision in USH1F patients.

In parallel, our team is also developing and investigating the impact of viral vector-based delivery of a normal copy of human *PCDH15* gene in the USH1F mouse retina. Initial experiments revealed very promising results and showed significantly better visual function in the USH1F mice that have received the normal gene copy. Our team is currently exploring the long-term preservation of visual function in these animals.

Livia Carvalho, PhD

University of Western Australia

The Retinal Genomics and Therapy lab led by Dr Carvalho at the University of Western Australia/ Lions Eye Institute, Perth, Australia, was able to secure extra funding in 2021 from the Channel 7 Telethon to continue their investigations into testing a dual AAV gene therapy for Usher 1F. Together with stem cell expert and collaborator Dr Carla Mellough, they have recruited a new student



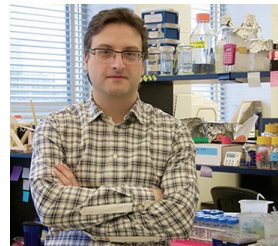
Carvalho lab

working on testing the Usher 1F gene therapy on retinal organoid cell model derived directly from an Usher 1F patient. During 2021 they were able to expand and grow Usher 1F retinal organoids in the lab and deliver the AAV gene therapy treatment. The final data analysis looking at protein and gene expression after treatment is currently underway.

Furthermore, following the already highly collaborative start of this project, which includes Prof Zubair Ahmed (University of Maryland), Assoc/Prof Luk Vandenberghe (Harvard University), Prof Alex Hewitt (University of Tasmania) and Prof Alice Pebay (University of Melbourne), Dr. Carvalho is also now working with Dr Anai Gonzalez-Cordero (Children Medical Research Institute/University of Sydney) investigating the effect of the Usher 1F dual AAV gene therapy on more mature retinal organoids carrying a different 1F mutation. This expansion will allow them to validate this therapy in Usher 1F lines from different patients, adding further confidence to the results.

Vincent Tropepe, PhD

University of Toronto



Vincent Tropepe

The cause of retinal degeneration in USH1F is still a mystery. Using zebrafish, we have developed one of the first genetic animal models with a clear USH1F retinopathy, and this model will enable us to understand how the normal molecular function of *PCDH15* leads to the production of healthy photoreceptors and typical vision. My lab has performed a detailed analysis of photoreceptor structure in animals with the mutation, and we find that the outer segments of these cells develop abnormally and often detach completely from the rest of the cell well before there is any evidence of cell loss. Funding from the USH1F Collaborative will allow us to explore two experimental approaches to molecularly repair the defective photoreceptors in our model. First, we will add back normal copies of the *PCDH15* gene to see if we can rescue the defects. Second, we will use gene editing technology to directly repair the mutated gene. In both cases, we will test if repaired photoreceptors can rebuild their normal outer segments and regain visual function. If successful, this research will point to a potential window of opportunity to use *PCDH15* gene therapy to repair photoreceptors at the onset of symptoms to prevent the progression of vision loss. ◆

Striving to Make Higher Education More Accessible for All

By Jessica Chaikof

Growing up, my parents always told me to never let my disability define or impede me. Even though I am now in my mid-twenties, I continue to live with this motto in everything that I do. As a person living with Usher Syndrome type 1F, I know firsthand the effect Usher 1F has on one's life. I have had to overcome numerous obstacles—teachers doubting my potential, exclusion from group activities, stereotypes associated with being deaf and visually impaired, and denial of accommodations that are critical to my success. Throughout my academic career, I have had to not only advocate for myself but also for others.

Students at my undergraduate institution embraced being an inclusive and diverse community, accepting of all types of people. Yet the challenge of living with a disability or fostering an environment that promotes accessibility was rarely part of the conversations about diversity. In addition, most students with disabilities do not wish to be publicly identified due to their desire to be accepted within the general student population. Utilizing my advocacy skills, I sought to change the conversation around diversity by emphasizing the ways in which a disability, at times apparent and in some cases hidden, can marginalize many students.

During my last two years of undergrad, I focused on not only working to bring forward the voices of students with disabilities by helping to create the first disability club on campus, but also centering my research around it. My senior thesis, *Faculty Perceptions Toward Accessibility in the College Classroom*, focused on understanding how accessibility shapes the faculty experience within the classroom. My research helped to identify significant barriers between students with disabilities and faculty, such as students needing to disclose their disability to receive accommodations when many do not; certain disabilities, such as chronic illnesses, are not recognized and create unpredictable challenges; and classroom practices to accommodate everyone, such as Universal Design, are not widely known by faculty. Faculty desire more information and support on working with students with disabilities. Consequently, there is a need for faculty to have access to as much information on accessibility as possible.

In my desire to continue this research, I have been attending American University for a master's degree

in sociology. Unfortunately, due to the coronavirus, my first year of grad school was spent on Zoom.

Prior to the start of classes, I was terrified of having to take class on Zoom, especially as a person with Usher Syndrome. I worried not only about being able to hear and see things on Zoom but also making connections with my professors and classmates. As the semester progressed, my worries eased as I got to know my professors through office hours and my classmates through impromptu Zoom happy hours. I fell in love with the program and felt incredibly supported by the sociology department at American.

During my time at American, I have met so many amazing professors, including one who was the first person to not only make me feel welcome at American but also showed me that there was something worth fighting for. Through the assignments for the class, she frequently encouraged me to not only pursue my research interests in accessibility and disability but also to think about other potential areas of research, such as chronic illnesses and the role gender plays in disability. Eventually, the two of us decided to work together on a research project examining the impact endometriosis has on college students, including how the pain affects their lives academically, professionally, and socially. There is so much information on support for other disabilities, such as ADHD, deafness, and vision loss but, unfortunately, limited knowledge for individuals with chronic conditions since they are invisible and contested illnesses. We need to be able to identify the barriers that these students are facing to determine how can we better support them.

Due to the availability of the COVID-19 vaccine, I have been able to attend my second year of graduate school in-person in Washington, DC. However, COVID restrictions, such as masking and social distancing, are still in place to protect us. As a person living with Usher Syndrome, these restrictions have proven difficult for me. Since the university does not offer graduate student housing, I have chosen to live in apartment that is less than a mile off campus. Unfortunately, most of my classes are at night, which is a



Jessica Chaikof with her service dog Jigg

challenge with night-blindness due to Usher 1F. The streets that I walk to and from my apartment are not well-lit, making it tough for me to see. When my family and I did a test run, I realized that I could not get home safely by myself at night. I contacted the accessibility services office and mentioned my vision, letting them know that I would need help getting back safely at night. Accessibility services told me that the school's public safety escorts would help me.

After my first night of classes, I called public safety asking for an escort, telling them that I am blind in the dark and could not see to get back to my apartment. They informed me that public safety did not have escorts for off campus and that I was on my own. I was upset and terrified because I did not feel safe that night. To make matters worse, my class was in a building far off the main campus. The only way for me to get home was through an Uber. Fortunately, my classmates stayed behind and made sure that I got into the correct Uber safely. After that night, the sociology department worked to move my class to a building that was more accessible and on the main campus. In addition, my classmates offered to walk me home at night to make sure I stay safe.

What has frustrated me the most about this incident is that accessibility services did not understand and would not help

me. Their suggestions included taking the DC Metro back to my apartment or using an app to have public safety track me, neither of which would work for me since I am blind in the dark. If I could, I would drive myself home at night but, unfortunately, Usher 1F has robbed me of the ability to drive and see at night.



View of Jessica's walk from campus with normal vision vs. with her night vision

I am incredibly fortunate to have such a wonderful and supportive department, but so many are missing the larger picture, that so many students with disabilities are struggling to obtain reasonable accommodations that afford us equal access to higher education. I plan to obtain a PhD in sociology so that I can conduct research that not only contributes to the sociological field but also helps to create and change institutional policies to ensure that higher education becomes more accessible to all students with disabilities. ♦

Read Meat Lover's Club - an Epic "Meating" for One of Their Own



Red Meat Lovers Club chefs and hosts

On September 29, 2021, the Red Meat Lover's Club, led by Evan Darnell, the Secretary of Steak, along with Ariane and Michael Duarte, held an amazing, enthusiastic fundraiser at Ariane Kitchen & Bar in Verona, NJ, in support of local resident Zachary Root, who has Usher Syndrome type 1F. Guests at the sold-out event were treated to a chef prepared meal by Ariane, which also featured

Bagels by Jarret, Gotham Burger Social club by Mike Puma, Honey's by Carrie Halper and Jola Coffee, followed by both a live and silent auction.

Zachary's parents and Usher 1F Collaborative board members, Jared and Rachel Root, spoke, thanking their friends for supporting them in the past by riding bikes, racing through mud, and making a bowl of cereal blindfolded, and now by eating steak. Joining them for the event were Usher 1F Collaborative founders and board members Elliot and Melissa Chaikof.



Emily, Rachel and Jared Root holding Zachary

Thanks to the generosity of the hosts and guests, the epic "meating" raised \$30,000 for Usher 1F research!

Missing Pieces *continued*

I am referred to another doctor, genetic testing, visits in different cities. There's no treatment, as of yet, just mitigation of symptoms. I learn that I am going blind. I learn that I have always been going blind, and I am nineteen years old.

My brother drops a figurine behind his bed, and I get on the floor to look. I can't see through the dark under his bed. I am nine years old.

I am asked to stand on one leg and hold my balance. I can't. I don't ride bicycles because I will wobble and fall. I am eleven years old.

I move through a crowd, or turn a hallway, and bump into people. I step to the side and smack my shoulder into a wall. I dent my shin on a low bulky bollard. I am thirteen years old.

I am hiking, and I need to cross a small creek, dry rocks a built bridge. I need to ask my friends to hold my hand to step across. I am fifteen years old.

I am watching a movie with my cousins. The theatre is dark, I move slow, and I lose them in the glare and noise. I sit alone for half the movie. I am seventeen years old.

I am going to the bars with my friends in the city. We're on the train. My friend yanks me by the back of my shirt and drags me out. I didn't hear or see them step off. I am twenty years old.

Right now, at twenty one, this is my life. I look up at the night sky, full of stars I can't see. I walk into a stranger who was always on my left. People call my name and I stand still, because it's easier if they come to me than it is to look for them. I wanted to be a detective, before I realised being deaf would limit me, and then a crime scene investigator. Now I can be neither, so I will work in an evidence analysis lab. I don't drive, so I use public transit, and curse the city for not etching its street names into the sidewalk because I can't read the signs.

I don't know what the future holds, what's coming in the next few years, but I want there to be something for me. Something that halts the degeneration, or something that restores my lost rods and cones, or some cybernetic eye to match my cybernetic ear. I don't want to lose more than I already have. ◆

Introducing Josh Cohen, Our New Board Member



New board member, Josh Cohen

Joshua Cohen is the President and CEO of Pearl Media. With over 20 years of experience in the media and advertising business, Cohen has continually embraced emerging technology to offer clients the latest in innovative communications content. His creativity and dedication has helped create groundbreaking campaigns for Fortune 100 brands, including Disney, GM, Tommy Hilfiger, Verizon, Miller Coors, ESPN, Sports Illustrated and Lexus.

Founding Pearl Media in 2006, Josh's innovation and experience has grown the company from a traditional outdoor media group to a creative minded and technology driven experiential agency.

Usher 1F Collaborative has been the fortunate recipient of Josh's skills in the past when he designed posters for our Sight.Sound.Cycle events. We are excited to welcome him to our board. ◆