USHER 1F
COLLABORATIVE

NEWSLETTER

Fall/Winter 2020

Rare As One grantees

Chan Zuckerberg Initiative Rare As One Project Grant

On November 25, 2019, we received an email with the exciting words,

> "We are very pleased to inform you that your application will be recommended for funding from the Chan Zuckerberg Donor Advised Fund (DAF)... We are very excited to welcome you as part of the Rare As One Network, and we look forward to supporting and learning with you as you work to develop and strengthen a patient-driven collaborative research network in your disease area."

We had to hold our tongues and sit on our hands until the public announcement on February 3, 2020. Much excitement, including press coverage, followed, and then it came time for us to get to work. The purpose of the grant is not to directly fund research but, rather, to enable us to grow and refine our organization, helping provide us with knowledge, tools, and resources to ensure sustainability so that we have the capacity to continue to fund the research until everyone with Usher 1F is cured.

While COVID forced the cancellation of our kickoff meeting in California with the Chan Zuckerberg Initiative (CZI) team and the other 29 grantees, as well as of our November 2020, meeting, utilizing technology such as Zoom, the resourceful CZI team has enabled us to gather and meet virtually, also providing speakers and mentorships that have been incredibly beneficial.

The first year of the grant included funding for us to hold an international research conference, which we had initially planned for October 2020. Once again, COVID forced a postponement. With large in-person gatherings still likely many months away, we will be hosting a virtual international research conference, Therapeutic Strategies for Large Protein Coding Genes in Usher Syndrome, in May 2021. We are very excited to host this gathering of top Usher Syndrome researchers, along with those in related fields doing work of benefit to Usher Syndrome. While the conference will feature our Usher 1F researchers and their work, it will also bring together those working on the other large Usher genes, with the goal of shared strategies, techniques, and ideas, resulting in collaborations that will help advance a cure not only for Usher 1F but also for the other types of Usher Syndrome caused, as is Usher 1F, by mutations in large genes.

Rare As One

The CZI grant has also enabled us to get help for our hard-working all-volunteer team, bringing on board Erica Miller, profiled in our Spring/Summer 2020 newsletter. Erica has been a tremendous asset with her energy and enthusiasm for our mission, combined with her knowledge and skills. Finally, thanks to CZI, we have access to tools that have enabled us to become a more professional and efficient organization.

We are incredibly honored and grateful for the opportunities the CZI Rare As One Project grant has provided us. The CZI team's belief in our mission and our work, combined with their ongoing education, collaboration, and resources, are proving invaluable. ◆

View from Oregon researcher Jennifer Phillips's window during the fire.

View from the same window after the worst of the fire was over.

Our University of Oregon Team Perseveres Through Two Incredible Challenges

The workplace shutdowns brought about between March and May by the COVID pandemic also included research laboratories at the universities where our Usher 1F research labs are housed. While COVID-19 has impacted all of our research labs, one of our labs, the University of Oregon Institute of Neuroscience in Eugene, Oregon, was affected by yet a second disaster, the out-of-control wildfires on the west coast.

The COVID shutdown for our University of Oregon lab lasted from mid-March until late May. During that period, Monte Westerfield, PhD, and Jennifer Phillips, PhD, maintained only a skeleton crew who took care of the fish and monitored essential laboratory equipment, but, otherwise, all on-campus research stopped. Beginning in May, they were able to return to the laboratory in a very limited fashion with personal protective equipment (PPE) and extensive monitoring protocols. In June, their access expanded, and they currently are allowed to operate at between 50% to 75% occupancy.

Fortunately, the lab did not lose any animals or research supplies, which would have been catastrophic, either enormously expensive to replace in bulk or even irreplaceable. The largest impact was on long-term experiments that involve raising and breeding genetic stocks of zebrafish. Because the fish weren't breeding for many weeks during the shutdown, they have been slow to return to pre-shutdown egg production.

The large Holiday Farm fire, which devastated the McKenzie River Valley, spread to within 30 miles of the group's laboratory and homes. The tongue of the fire shown in red in the photo, was 2o miles away from the neighborhood that borders the university. According to Dr. Westerfield, "the smoke here was so bad the streetlights were on during the day."

While our Oregon team was not placed in evacuation mode, the smoke and ash were very hazardous. The air quality reached 500 on a scale that tops out at 500. The University and surrounding community were advised not to go outdoors without an N95 mask. Because University buildings are currently using 100% outside air to maximize air turnover during the COVID pandemic, this meant that it was also very hazardous to enter the laboratory. All staff except animal care workers stayed home.

Dr. Phillips was faced not only with working from home but also with her mother's memory care facility evacuating due to the fires. For five days in September, Dr. Phillips became her mother's fulltime caregiver, squeezing in her research correspondence late at night and early in the morning while her mother was sleeping.

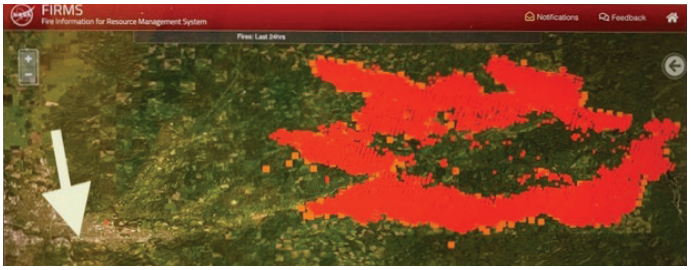
By late September, the team was back in the laboratory with outside air quality at 54, which is considered moderate. The cooler, wetter weather is helping to slow the fires, with the hope that the fall rains will completely extinguish them.

Despite the interruptions caused by COVID and the wildfires, our wonderful University of Oregon team still made

progress. During the months prior to the COVID shutdown, they analyzed the Usher 1F zebrafish, characterizing their hearing, balance, and vision in order to understand the different effects of the various types of mutations. Once they were able to return to their laboratory in June, they began tests of a potential small molecule therapy that might slow or stop retinal degeneration in the zebrafish models. By testing a number of different concentrations, they were able to identify an optimal treatment dose.

Our Oregon team's objectives for 2021 include testing the optimal dosage of the small molecule in the Usher 1F zebrafish to evaluate whether there is improvement in their photoreceptor health. They are also planning a new set of studies that may lead to an antisense oligonucleotide (ASO) therapy. This type of therapy is in clinical trials for Usher 2A, and the team is developing a strategy that will allow them to test ASOs as a therapy for Usher 1F.

Our Usher 1F research team at the University of Oregon has demonstrated to us year after year their amazing ability to stretch a dollar. When telling Dr. Westerfield and Dr. Phillips of the launch of our Ten to Cure initiative (*see article page 6*), we asked them what a major sum of money would mean for Usher 1F research. They both said without hesitation that it would significantly enhance and speed their progress, enabling them to, according to Dr. Westerfield, "start more expensive studies that require specialized equipment and supplies that we currently cannot afford." Dr. Phillips added, "In the five years of support we have received from the Usher 1F Collaborative, we have maximized our resources to develop effective and efficient tools for the study of USH1F but have been limited in the scope of what research questions we are able to pursue due to the prohibitive cost of high tech analyses as well as the limits of the small research staff. A bulk infusion of funds would dramatically expand the range and potential of our USH1F work." ◆



Satellite map showing proximity of fire (red) to our Usher 1F lab at the University of Oregon (white arrow).

Research News

David Corey, PhD, Harvard Medical School, presented his Usher 1F work at the Usher Syndrome Coalition virtual conference in July 2020. He described his work developing a mini gene, that is a gene with pieces not essential for vision removed so that the entire remaining gene would fit on the conventional delivery method for gene therapy, an adeno-associated virus (AAV). We are excited that this approach is restoring hearing in a newborn Usher 1F mouse, and Dr. Corey is now testing the mini gene on our Usher 1F zebrafish that he obtained from our University of Oregon team to see if it restores vision.

Zubair Ahmed, PhD, University of Maryland, is in talks with two biopharma companies, the first to determine if their compound, a translational read through inducing drug, will be effective in restoring vision in those with Usher 1F. He is in talks with a second biopharma company about testing their state-of-the-art approach to gene therapy using dual AAVs with inteins.

Monte Westerfield, PhD, and Jennifer Phillips, PhD, University of Oregon Institute of Neuroscience, are collaborating with a Dutch Usher Syndrome research team, headed by Erwin van Wyk, PhD, Raboud University Medical Center, to test exon skipping for Usher 1F using antisense oligonucleotides. This research is similar to a treatment from ProQR already in clinical trial for Usher Syndrome type 2A. ◆

Introducing Our Usher 1F Scientific Advisory Council

Almost seven years ago, Usher 1F Collaborative was founded with the explicit goal of finding an effective treatment to save or restore the vision of those with Usher Syndrome type 1F. Since then, there has been prolific scientific research thanks to the almost 5 Million dollars contributed by generous donors.

Step by step, progress has been steadily advancing in our laboratories. Just one year after being established, over six figures of funding had already been delivered to a lab at the University of Oregon. Within the first two years of our existence, we had not one, but two animal models; a zebrafish and a mouse. In our quest to develop and test a treatment, we have seen great strides since the development began of gene, drug, and stem cell therapies in 2016. Just this year, zebrafish vision gene therapy testing began, and significant progress with gene therapies has been made, including restoring hearing in a mouse model.

None of this would have been possible without the researchers who devote their work to our mission. Recognizing the integral role that scientists play in the hunt for a treatment, Usher 1F Collaborative has decided to form a Scientific Advisory Council. This body of three will provide strategic guidance and will advise on timing and implementation of proposals. We are thrilled to announce that our Scientific Advisory Council will include the following members: David R. Liu PhD, Aravinda Chakravarti PhD, and Richard Cummings, PhD.

David Liu, PhD

David R. Liu, PhD, Harvard Department of Chemistry and Chemical Biology, is the Richard Merkin Professor, Director of the Merkin Institute of Transformative Technologies in Healthcare, and Vice-Chair of the Faculty at the Broad Institute of Harvard and MIT; Thomas Dudley Cabot Professor of the Natural Sciences and Professor of Chemistry and Chemical Biology at Harvard University; and Howard Hughes Medical Institute Investigator.

Liu graduated first in his class at Harvard in 1994. He earned his PhD in 1999 and became Assistant Professor of Chemistry and Chemical Biology at Harvard University. He was promoted to Associate Professor in 2003 and to Full Professor in 2005. Liu became a Howard Hughes Medical Institute Investigator in 2005 and joined the JASONs, academic science advisors to the U.S. government, in 2009. Professor Liu's research integrates chemistry and evolution to illuminate biology and enable next-generation therapeutics. He is the scientific founder or co-founder of seven biotechnology and therapeutics companies, including Editas Medicine, Pairwise Plants, Exo Therapeutics, Beam Therapeutics, and Prime Medicine.

Aravinda Chakravarti, PhD

Aravinda Chakravarti, PhD, NYU Grossman School of Medicine, Director, Center for Human Genetics and Genomics, Professor, Institute for Systems Genetics, Professor, Department of Medicine, is a molecular geneticist whose research is aimed at genome-scale analysis of human disease, analysis of gene variation and function, and elucidating the genetic basis of common genetic disorders. He received his PhD in human genetics from the University of Texas Health Science Center in Houston in 1979 and continued postdoctoral training at the University of Washington in Seattle until 1980.

He was the 2008 President of the American Society of Human Genetics (ASHG) and has been elected to the US National Academy of Medicine and is a Fellow of the AAAS. Dr. Chakravarti is one of the founding Editors of Genome Research and the Annual Reviews of Human Genetics & Genomics. He received the American Society of Human Genetics' Allan Award in 2013 for his contributions to human genetics.

Richard Cummings, PhD

Richard Cummings, PhD, the S. Daniel Abraham Professor of Surgery at Beth Israel Deaconess Medical Center (BIDMC) and Harvard Medical School, is the BIDMC Surgery Vice Chair, Basic and Translational Research; Director, National Center

for Functional Glycomics; Director, Harvard Medical School Center for Glycoscience; Chair of the BIDMC Research Council. As of 2018 Cummings is also the Scientific Director of the Feihi Nutrition Laboratory at BIDMC and Director of the Cancer Glycomics Program within the Cancer Research Institute at BIDMC. Before moving to BIDMC/HMS, Cummings was the William Patterson Timmie Professor and Chair of the Department of Biochemistry at Emory University School of Medicine in Atlanta, Georgia, from 2006-2015. At Emory, Cummings was a founder in 2007 of the Emory Glycomics Center.

Please read the full biographies of these three amazing scientists on our website:

usher1f.org -> About Us -> Scientific Advisory Council

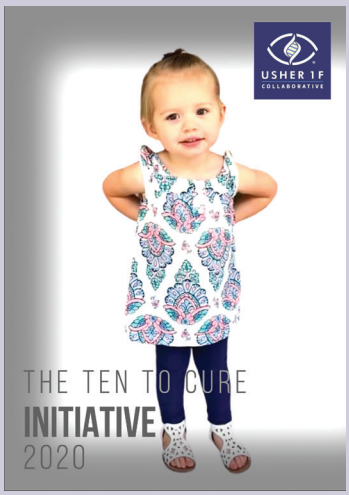
We welcome all three members to the Scientific Advisory Council and extend our deep appreciation for their contribution of their valuable time and knowledge. We look forward to the successful completion of a treatment in the lab, leading to the preclinical stage, and subsequently, a clinical trial. With our ever-growing Usher 1F community, we are even closer to making our vision a reality. ◆

Ten to Cure

The Usher 1F community is excited to announce a new major gift initiative called "Ten to Cure!" The name alludes to the campaign goal of raising $10 Million in new money to catapult research to the next critical levels for new breakthroughs.

Through several weeks of research, development, planning, and execution, the "Ten to Cure" initiative is ready for launch! Prospective donors have been identified, and strategic plans for the trajectory of each have been created. The team will be working with members of our board to network with donors in your geographic area and develop those relationships. Through this multi-city reach-out model, we aim to utilize various methods to present our case to potential donors. Considering the impact of the Coronavirus, we plan to supplement local networking with virtual gatherings. We look forward to hosting you for virtual information sessions, and we look forward to you sharing these virtual information sessions with your network as well.

We owe a tremendous debt of gratitude to Berman Branding, founded and run by Rebecca Berman (friend of Jared and Rachel Root), who crafted a profoundly compelling visual brochure for us (see https://www.usher1f.org/ten-to-cure.html). Rebecca is also the same person who created our new Usher 1F Collaborative logo. Our brochure is a digital document which can also be printed and delivered as a stunning presentation. The brochure opens by communicating the problem that those with Usher 1F face and immediately asks the reader to imagine if we were able to find a cure. There are quotes and first-person testimony about living with Usher 1F, helping the reader empathize with individuals and families. The brochure also paints a picture for potential donors to understand what we have already accomplished and what our future plans are. Finances are clearly laid out, allowing individuals to understand exactly where their money will go.



The cover of our Ten to Cure Initiative featuring adorable Andi Picanzo, who has Usher 1F.

It states in the brochure that, "The right design & strategy - with an incentive system to achieve the required patient outcomes is key to our success. Combined with motivation & urgency, along with talent, resources and continuity, our team has the essential ingredients." We are glad to feature our Board of Directors, lead scientists, engineers & researchers, and our Scientific Advisory Council; our digital brochure even links to individuals' bios on the Usher 1F website!

We thank you for your commitment and look forward to your engagement with this new initiative. Ten to Cure can and must #UsherInTheLight and we cannot do this without you! ◆