
Rebecca Alexander

USHER III INITIATIVE

Newsletter

Featuring a Profile on Dynamic Usher III Patient, Rebecca Alexander

A Letter from Cindy Elden

Co-founder, Usher III Initiative


Cindy Elden

Dear Friends,

Hello! I would like to extend a special **welcome** to the newest friends of the Usher III Initiative! We communicate the latest developments in our research and advocacy activities through our newsletter. I hope you find the information helpful and are inspired to join us in our efforts!

2013 has been a busy year for our team as we forge ahead toward a treatment for Usher III. During the first quarter, several funded research projects were scheduled to conclude. In early May our research team, Scientific Advisory Board and leadership met to discuss the latest results from our small molecule and gene therapy researchers. The Initiative's scientific advisors, with input garnered from our peer review process, then developed the best plan to achieve a definitive proof of concept in the next twelve months.

Our research efforts are described in detail later in this newsletter, but here are some highlights:

- We tested six small molecule compounds we created that have the potential to preserve Clarin1, which is necessary for proper vision and hearing function. Our tests focused on the efficacy and safety of these drugs. We have selected the four most promising candidates and are designing a new proof of concept protocol for these candidates.

- We are incredibly excited to report that the first functional retinal phenotype was found in Usher III mice! The deficiency was noted by Yoshi Imanishi at Case Western Reserve University in animals at a more advanced age than those previously tested. Yoshi and his team will continue to investigate the retinal function in these and other mice to determine whether the mouse model

is reliable for use in future drug testing.

- Another very exciting development was that Clarin1was successfully retained in the cells of animals treated with one of our compounds. While this does not prove functional effect (i.e. that retinal function does not degrade), this is the first *in vivo* work that shows that these compounds do, in fact, stabilize Clarin1, which has long been a goal of ours.

- We are pleased to welcome a new researcher to our team! Dr. Lawrence Lustig, a Professor in the Otolaryngology Department of the University of California San Francisco School of Medicine, is accomplished in rescuing hearing in mice using AAV vectors. The Initiative is always looking to work with researchers who might help expedite the development of a treatment, and we're delighted Dr. Lustig has joined our gene therapy program.

Our primary goal for the next 12 months is achieving proof of concept in either or both the gene therapy and small molecule paths. This proof of concept validation of our research is critical to move forward to the FDA for clinical trial.

When it is time to seek FDA approval of trials, the more information our team has on the number and geographic location of patients, as well as clinical data on them, the better our chances for a speedy review! To this end, we are continuing our coordination with the Coalition for Usher Syndrome Research (www.usher-syndrome.org) and our support for the Coalition's Usher Syndrome Registry (www.usher-registry.org). Since the registry was launched more than a year ago, over 29 families from 8 countries (Australia, Canada, Denmark, Germany, Israel, Netherlands, UK and US) have volunteered information about how Usher III affects them. A Spanish version of the registry has already been launched and a Hebrew version (thanks to the efforts of Yael Saperstein and others) will be launched later this month. Have you registered?

As you know, this patient registry is critical to research initiatives like ours. We need you and your family members and friends who are affected by Usher Syndrome to help us and other research efforts move quickly and efficiently forward. If you have not yet registered, please do so today on the safe and confidential registry. We need everyone afflicted with all types of Usher to register! Again, the link is www.usher-registry.org.

Thank you for your interest and support!

Warm regards,

Cindy

We are at an exciting point in our research, with the goal of achieving proof of concept for two potential treatments during the upcoming year. Time is of the essence for Usher III patients who continue to lose vision and hearing with each passing day. Please join us in our efforts to stop this deaf blinding disease by making a donation to support our research.

We are at a critical point and your support now will really make a difference!

Please visit www.usheriii.org/donate or mail your check payable to the Usher III Initiative to the following address:

Usher III Initiative
191 N. Wacker Dr., Suite 2090
Chicago, IL 60606

More research highlights from this year…

Our team met in May of this year and reported some very exciting progress.

We continue to optimize, refine, and test a number of compounds that have the potential to stabilize defective Clarin1. Over the last several years we have funded extensive work on those compounds at a laboratory in the UK to better understand their chemical composition, potential toxicity and other factors in preparation for potential FDA trials. Additional follow-up studies will be completed by February 2014.

At Cleveland's Case Western Reserve University, important work continues on several fronts:

· Proof of concept testing of the four leading compounds is being led by Dr. Kumar Alagramam at Case. Dr. Alagramam is testing our compounds in mice with the Usher III hearing phenotype to determine if we have a positive proof of concept (i.e. that the compound is actually stopping or slowing the progression of deafness in the mice). The testing is complex and each successive round of tests has built on our previous knowledge base as we learn more about the compounds and their effect on the animals.

· Dr. Alagramam will also develop a transgenic mouse that shows hearing loss later than the mice we currently have. We have found this additional mouse model development to be necessary because our compounds have proven to be too strong for neonatal mice. Previous studies have shown that the compounds are well tolerated by older mice. Dr. Alagramam is using knowledge and proficiency he has gained through his extensive Usher III research over the past several years and we remain hopeful that the combination of more refined compounds, enhanced knowledge of their effects, and administering the compounds to older mice will result in successful proof of concept.

· The first functional retinal phenotype was reported earlier this year in Usher III mice developed through a long-term project at contract research laboratory engaged by the Initiative. Many thanks to the Smart Family Foundation for funding this project! The retinal deficiency was noted via ERG (electroretinography) testing in Dr. Yoshi Imanishi's lab at Case Western Reserve University in animals at a more advanced age than those previously tested. The animals were specifically developed for this purpose - to see how the disease progresses with age. Dr. Imanishi and his colleagues will further investigate the retinal function in these animals to determine how reliable the model is for future drug testing.

· Dr. Imanishi also continues his work to better understand how our small molecule compounds interact with Clarin1 protein. Dr. Imanishi established that Clarin1was successfully retained in the cells of tadpoles exposed to one of our compounds. While this does not prove that retinal function is preserved, this is the first *in vivo* work that shows that these compounds stabilize Clarin1. Understanding how these molecules work will help us develop and optimize the compounds as therapeutics. It will also give us an indication of a broader spectrum of diseases that may be helped by our compound, making the compound potentially more attractive to traditional pharmaceutical development.

In addition to our traditional drug research through the small molecule project, we continue to pursue a multi-strategy approach with the gene therapy research led by Bill Hauswirth's lab at the University of Florida. Dr. Hauswirth's team was not able to conclusively establish a visual phenotype in the mouse model based on reactions to light exposure, as was his previously stated goal, but they have been working closely with Dr. Imanishi to replicate the retinal phenotype in the ERG of older mice. The team plans to use that model to test their gene therapy treatment. At the same time, they have developed additional vectors that they and other labs will use in testing.

Finally, we added a new researcher, Dr. Lawrence Lustig at University of California San Francisco, to our ranks this year! We are very happy to have Dr. Lustig's lab on the team and their work in auditory gene therapy is showing great promise. The Initiative approached Dr. Lustig after reading about his success in rescuing hearing after performing a very delicate procedure to place an AAV vector in young mice with hearing loss due to a different genetic disease. A link to the publication about that effort is provided below. We are hopeful that, if successful in rescuing hearing in an Usher III model, Dr. Lustig's work can augment or, if necessary, substitute for, successful proof of concept testing in a retinal model.

We want to thank those of you who have supported our efforts in the past. We hope that this newsletter presents compelling evidence for our research model and the scientific strides we have made in such a short time. We are determined to achieve our goal of developing a treatment in the fastest, most efficient way possible.

Once we embark on full scale pharmaceutical production in order to achieve our goal, it will require more resources than ever. We hope that you are inspired by how close we are to a real treatment for Usher III patients and that you will join us and be part of our success and a cure to Usher III.

Ways to get involved!

The Usher III Initiative's top priority is to develop a treatment for patients with Usher III. Our goal is to begin clinical trials in 2014. In order to achieve this goal, patients should begin to plan for these trials now. Because Usher III is an orphan disease which does not affect a large population, it is important that each and every patient join our efforts to prepare for clinical trials. Early gathering of patient information will put us in a strategically better position to get to trials faster.

WE URGE ALL USHER III PATIENTS to take the following steps to be the most proactive patient you can be:

1. **JOIN THE USHER SYNDROME REGISTRY** which was launched online by the Coalition for Usher Syndrome Research. The patient registry is critically important to clinical trials. You can access the registry at www.usher-registry.org. If you have already registered and would like to help advance the prospects of full participation by all Usher patients in the registry, please share information about it with your contacts. This includes all patients, relatives of patients, caregivers, advocates and support organizations that interact with patients such as schools, clinics, rehabilitation centers, etc. The more data in the database, the more powerful it is in terms of providing valuable information to researchers, funders and government agencies! A Spanish version of the database has already been launched and Hebrew is on its way, many thanks to the efforts of Yael Saperstein! French, Dutch and German are also coming.

2. **GET GENOTYPED**. We encourage all Usher Syndrome patients to find out specifically which gene is causing their Usher disease. Many people with Usher have only received clinical diagnosis (this means diagnosis based on your symptoms and not based on a definitive blood test). As a result, some Usher patients have been misdiagnosed as Usher II when a blood test and genotyping may reveal they are actually Usher III. The only way to know for sure is to be screened for one of the many genes that can cause Usher disease. Screening can be done through a medical geneticist locally or through one of the following organizations:

The John and Marcia Carver Nonprofit Genetic Testing Laboratory
University of Iowa
Bill Kimberling, Ph.D.
https://www.carverlab.org/projectusher/instructions

Mount Sinai Center for Jewish Genetic Diseases
Michelle Cahr, MS, CGC
(212) 241-6947
http://www.mountsinaifpa.org/

Harvard Medical School and Partners Healthcare
Heidi Rehm, Ph.D., FACMG
(617) 768-8500
http://pcpgm.partners.org/lmm/tests/hearing-loss/usher

If you would like assistance in locating a genetic testing facility, please contact our office via e-mail at info@usheriii.org or by phone at (312) 896-2509.

Check out these recent publications by our researchers!

Ruishuang Geng, Yoshi Imanishi, Kumar Alagramam, et al, "The Mechanosensory Structure of the Hair Cell Requires Clarin-1, a Protein Encoded by Usher Syndrome III Causative Gene," The Journal of Neuroscience, July 11, 2012.

Omar Akil, Lawrence Lustig, et al, "Restoration of Hearing in the VGLUT3 Knockout Mouse Using Virally Mediated Gene Therapy," Neuron 75, July 26, 2012.

Rebecca Alexander

Spotlight on…

REBECCA ALEXANDER

The Usher III Initiative relies heavily on friends and supporters to spread the word about our research and help us maintain the momentum that will bring us to a cure. One of our most loyal supporters is Rebecca Alexander, a Californian living in New York. Diagnosed with Usher III as a teenager, Rebecca, now 34, is determined to prove that individuals with this disorder may have physical disabilities, but can take on physical challenges that even seeing/hearing individuals might never attempt. Rebecca's drive and resilience are infectious and here are some of the many faces of Rebecca that make her our role model:

• Multi-faceted, career professional – A Columbia University educated psychotherapist with a thriving, private practice in Manhattan, Rebecca also has a large following among those who take one or more of her 10 spin classes (exercise classes on the stationary bicycle) each week.

• Extreme athlete – Most recently Rebecca has been participating in Civilian Military Combine (CMC), a new type of ultimate fitness competition that involves team participation in a series of boot camp exercises, participating in 3 to 7 miles of military inspired, obstacle course racing. Civilians team up with military personnel and first responders in this ultimate test of physical and mental endurance. Rebecca's latest "urban assault" competition was in Brooklyn earlier this month.

• Fundraiser – Rebecca's tireless efforts and those of her family and friends raised over $100,000 for the Usher III Initiative's research effort. Through the "Spin for Sight" event that Rebecca organized in 2012, celebrity participants Katie Couric (ABC) and Hoda Kotb (NBC) helped Rebecca bring awareness to the urgent needs for treatments and a cure for Usher III.

• Storyteller – If you haven't already seen Rebecca featured on TV (NBC's Today Show and local ABC news spots) and radio (several New York stations) or in print (Marie Claire and New York Magazine), you'll have a chance to read her upcoming memoir to be published in 2014 by Penguin Books!

• Usher III patient – With her hearing declining rapidly, and prompted by the dramatic results experienced by others, Rebecca had cochlear implant surgery on May 15th. Her new implant was activated on June 11th. Since that time she has worked diligently on mapping and listening therapy. "Sometimes just living life feels exhausting," says Rebecca, "but getting my new implant has made a huge difference in my daily quality of life. And… it's still improving every day!" As she re-learns how to hear through the computerized implant, statistics bear witness to the value of her efforts. With 28% hearing discrimination pre-operation, her most recent results are already at 76%! And though her vision continues to decline, this hasn't slowed her down. She's already planning her next challenge…so, stay tuned!

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Looking Ahead…

- **Usher III Initiative's next meeting**…The Initiative plans to conduct its next scientific working group meeting in May 2014. We look forward to reporting news from this meeting in our next newsletter.
- **Email updates**…If you are not currently on our mailing list would like receive updates and exciting newsflashes via e-mail, please visit our website (www.usheriii.org), provide your e-mail address and click on the "Get Notified" button.
- **Facebook**...Another way to stay in touch with us and other Usher III patients and families is via our Facebook page. Please "like" it at this link and you will receive notification of our posts via your newsfeed.
- This just in from our friends at The Coalition for Usher Syndrome Research…the **Third International Symposium on Usher Syndrome** (in conjunction with the Sixth Annual Usher Syndrome Family Conference) will convene in Boston, Massachusetts on July 10-11, 2014, bringing together researchers, clinicians, geneticists and specialists to present the latest research and developments on Usher Syndrome. The meeting will enable the exchange of ideas and knowledge among different disciplines in order to facilitate new research and progress that focuses on Usher Syndrome. The annual family conference will follow on July 12th. Click here for more details!

Contact Us…

We would love to hear from you! Please feel free to contact us with any questions or comments:

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By Email…info@usheriii.org