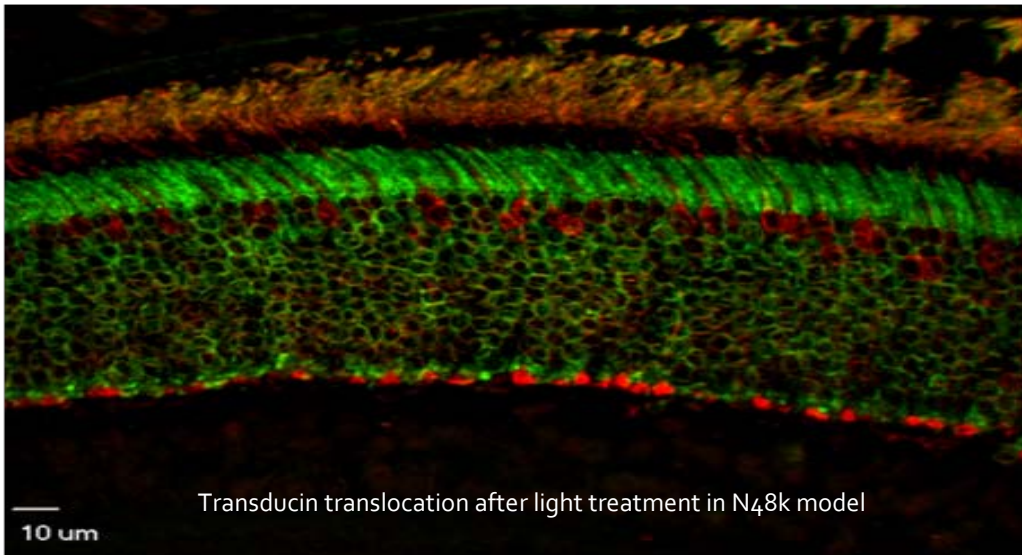

Transducin translocation after light treatment in N48k model

USHER III INITIATIVE

Newsletter

Featuring a Profile on the newest member of our research team, Dr. Lawrence Lustig

A Letter from Cindy Elden

Co-founder, Usher III Initiative

Dear Friends,

Welcome to the latest installment of the Usher III Initiative's newsletter! We are excited to update our supportive Usher III community on our research and other activities in 2014. The Usher III Initiative's dedicated team of researchers has worked hard and this year they have produced some great progress. I hope after reading the below that you will share my enthusiasm and respect for our team and all their dedicated efforts to develop a treatment for all of us with Usher III.

Each one of our researchers has achieved major breakthroughs in his research this year and we are excited in anticipation of their forthcoming publications.

Read below about our highlights this year. They include a successful proof of concept with gene therapy preserving hearing in mice with Usher III which is detailed in the fascinating interview with Larry Lustig at Columbia who has been at the helm of this groundbreaking research.

Also please be sure to note the update from Kumar Alagramam at Case Western, who has also shown proof of concept preserving hearing in mice using the small molecule we have developed.

As always we encourage you to get involved and join our efforts. To those of you who have supported us in the past, we thank you and are grateful for your generosity and support. We also hope you will find the updates below compelling and will continue to support our efforts as we move forward in new, exciting directions.

We started the year with a clear mission: To achieve positive proof of concept in an animal model using our novel drug compound, gene therapy, or both. We achieved this goal. Specifically:

- Following enhanced toxicity testing of our remaining four small molecule compounds which concluded in early 2014, Kumar Alagramam at Case Western Reserve University commenced testing the lead compounds in a specially developed mouse. He was able to prove efficacy of the compound in virtually all animals tested. These results indicate that the novel compound that the Usher III Initiative created and owns the intellectual property to, is able to stabilize hearing loss in mice at an early age.


Cindy Elden

- Another exciting development at Case was in Dr. Yoshikazu Imanishi's lab. He discovered the major proteins that interact with our small molecule and details about their interaction sites. This information helps us better understand the protein Clarin 1 and the characteristics of Usher III. This knowledge will help us develop and test treatments.

- We have had compelling results on the gene therapy side, as well. In Florida, researchers in William Hauswirth's lab

have had promising, though not yet conclusive, results in gene therapy treatment in the eye. The lab continues research to confirm the results.

- Lawrence Lustig, formerly Chief of the Division of Otology and Neurotology at the University of California San Francisco and now Chair of the Department of Otolaryngology/Head and Neck Surgery at Columbia University in New York, successfully preserved hearing in Clarin 1 knockout ("KO") mice using a gene vector delivered to the cochlea. This achievement was the result of exemplary cooperation among the UCSF, UFL and Case Western labs. (You can learn more about Dr. Lustig's exciting work in the interview with him later in this newsletter.)

Our efforts now that we have positive proof of concept in the mouse for both gene therapy and small molecule are to identify an industry partner who can develop these discoveries for use in patients.

This year the Usher III Initiative took part in the Partnering for Cures conference in New York City organized by Faster Cures. This conference provided us with the opportunity to learn from other medical research organizations like the Initiative that are further along on the treatment development process. We spoke to potential pharmaceutical and venture capital partners who are interested in developing treatments for orphan diseases like Usher III. We look forward to following up with the many contacts we made through this conference.

Additionally in trying to get the word out we are supporting our researchers' efforts to move ahead with publications and generate more exposure and excitement of all that our Usher III team has accomplished. We were also proud to sponsor the Usher Coalition's 2014 International Symposium on Usher Research in Boston in July.

The most important thing that our Usher III community can do to help us attract a pharmaceutical partner is to make sure that every single person you know who has Usher III is on the patient registry. The Food and Drug Administration (FDA) and potential industry partners would require adequate access to a number of patients for clinical trials. An identifiable patient population is important in attracting interest from the pharmaceutical industry and obtaining FDA approval to move into clinical trials.

Our mission is to put this research forward to the industry, and we need your help to move this ahead!
If you have not already, please go to the link below and enroll on the patient registry! www.usher-registry.org

We continue to make efforts to broaden our database and patient group by trying to find those who have not only been diagnosed, but those who may have been misdiagnosed as having Usher II rather than Usher III. We continue to advocate for patients to be tested (genotyped), if they have not been already.

Additionally this year we sent an email to over 1,000 doctors in major metropolitan areas of the US informing them about our organization and asking them to order genotyping for all potential Usher patients. For those patients diagnosed with Usher, we asked the doctors to encourage patients to visit the Usher registry. We also updated our website (www.usheriii.org). If you haven't visited it recently, please take a look!

This is an area where YOU can help! As the year comes to a close, please consider which of your contacts can HELP us in our mission to spread the word. Please forward this newsletter, share our new website (www.usheriii.org), "Like" us on Facebook (www.facebook.com/Usher3Initiative), or Tweet about us on Twitter (www.twitter.com/usheriii). It has been a productive year, and we hope you will continue to support our efforts at the Usher III Initiative.

We wish you and your family a wonderful holiday season and a happy healthy new year.

Thank you for your continued interest and support!

Warm regards,

Cindy Elden

We welcome your support, once again..

Now that we have proof of concept for two potential treatments for Usher III, we must continue to get our research to a pharmaceutical partner. 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.

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

Dr. Lawrence Lustig

Spotlight on…

Lawrence Lustig, MD

We stole a few moments of Dr. Lustig's time this month to speak with him about the exciting results he and his Usher III research team have achieved and his new positions as Chair of the Department of Otolaryngology/Head and Neck Surgery at the Columbia University College of Physicians and Surgeons and Otolaryngologist-in-chief at New York-Presbyterian Hospital/Columbia University Medical Center. Here are a few of the highlights of our discussion:

You have recently moved from San Francisco to New York. Can you please tell us about your new role and your goals for the near future?
I left a very good job in San Francisco where I was division chief of a strong division and I was enticed to come to New York. Columbia is a great institution, a world class hospital with NY Presbyterian; it's a great research institution and I saw an opportunity to take a smaller department and bring it up to the standards that Columbia deserves. That includes hiring a number of new faculty who will be involved in clinical trials and in translational research, as well as hiring a number of Ph.D.s who will be involved in more basic science research and trying to create a collaborative group where research can flow more seamlessly between the bed to the bench-top and back again.

How did you personally decided to focus your work on deafness and gene therapy?
I've been interested in hearing ever since I was a medical student. I took some time off and worked in a research lab for a year when I was a medical student. That research involved some of the basic science around cochlear implantation. Then I chose a fellowship at Johns Hopkins that allowed me to do a dedicated year of research in basic auditory physiology. The initial part of my research career at Johns Hopkins was focused on understanding the basis of efferent neuronal transmission and outer hair cell function of the inner ear. That was going well and I took that work back to UC San Francisco when I was recruited to become the division Chief of Otology and Neurotology. Then we were collaborating with a group in the Department of Neurology who were looking at a particular protein called vesicular glutamate transporter 3 (VGLUT3). A member of my lab, Omar Akil, had the idea to try to do some gene therapy studies to rescue the hearing. In these surprisingly successful studies, we had the first model of inherited deafness in a mouse where we were able to rescue hearing essentially back to normal. That led us to pivot our entire focus from basic science to translational projects attempting similar gene therapy rescue in other models of deafness. We still do some of our basic stuff in the lab but for the last couple years we have been focusing our research on gene therapy or genetic forms of hearing loss and looking at a number of different mouse models for that.

How does gene therapy work?
The basic premise of gene therapy is to take a bad gene and replace it with a good gene. There are a number of techniques to do this. One thing you have to think about is the vector, which is how you are going to get that gene into the cells. There are a number of different ways to do that but the most common is to use a virus. There are various kinds of viruses you can use. We've been using the adeno-associated virus (AAV). You take the gene that you want and put it in the AAV and you let it infect the cells. Then the virus injects the DNA into those cells and the cell starts cranking out the normal protein.

What is exciting about the data you have presented on gene therapy in the Usher III mouse model?
What we're really excited about is we've got this model where, if we can intervene with the gene therapy before the hearing loss occurs, we can either prevent or delay the onset of the hearing loss. What we've seen now in this as well as other models of genetic deafness is that if you try to intervene after the damage occurs in the inner ear and leads to hearing loss, the therapy doesn't help. Once the damage happens, we can't regrow those cells.

What we think we can do at this stage is, if we can intervene before the damage occurs, we can prevent that damage from occurring and, therefore, preserve the hearing. And when Kumar Alagramam created that mouse model that had a delayed onset of hearing loss, which is a little more similar to what we see in humans, by intervening before the onset of hearing loss we were able to preserve hearing in many of those mice. Not all of them, but many. That in and of itself is really exciting because it means that if we can perfect this technique and we can intervene soon enough in humans we might be able to prevent the hearing loss that otherwise would be occurring.

What are the next steps that would need to be done to get this to humans?
We don't have hearing preservation in every single mouse. It seems to be variable. Why there is this variability is still not clear. We don't know why some mice do great and some mice continue to lose hearing so we need to study that a little closer to try to figure out why - are we not getting enough virus to the cells they need to get to? Are there better viruses that can get more specifically to the cells we need to get them to? You know, Usher's is an outer hair cell problem - the virus that we're using is really good at inner hair cell delivery and not as good with outer hair cell delivery. So if we can find a virus that gets us better delivery to outer hair cells, that would likely lead to better hearing restoration. Also, we need to figure out if we can repeat the treatment these mice and keep the therapy going for longer and give us much longer term hearing results. Once we've perfected this in the mice we can really start doing it in the humans but I would really like to see much higher percentage recovery in the mouse before we move into humans.

How would gene therapy in the ear be delivered in humans?
There actually is a study that is being started by Novartis right now for gene therapy for hair cell regeneration. We [Columbia University] are one of three centers in the country that are going to be involved in that. The way we're delivering that therapy is to actually make a tiny little hole through the base of one of the middle ear ossicles, the stapes bone, and inject it into the inner ear that way. Another option of injecting this medicine is to insert it through the round window membrane of the cochlea, a little membrane that we can access through the middle ear. We do therapy to the ear all the time. We inject medicine into the ear and let it diffuse into the inner ear - things like steroids, and antibiotics like gentamicin to treat various forms of hearing loss or vertigo. We can put cochlear implants into the ear. So we have a number of ways we can get medicines and devices into the ear. I think ultimately it's just going to involve a direct injection technique. I don't think the delivery part will be challenging at all. The hard part is really going to be developing the right vectors and the right genes and figuring out the best timing of treatment.

Is this the first successful gene therapy in the ear?
There have been a number of gene therapy basic projects in the ear in animals. Most of the earlier studies were focused on hair cell regeneration - work out of the University of Michigan and University of Kansas and that was back in 2003-2006. And that is really what's led to the hair cell regeneration gene therapy trial that's going right now. So you can see it's been more than a five year timeframe to get from the bench to actually trying this in a phase 1 FDA trial in humans.

For genetic forms of deafness we've had probably one of the first successful gene therapy studies with the VGLUT3 gene in an animal model. Since then there have been a couple other studies that have shown for example another form of Ushers using antisense oligonucleotides injected into the peritoneum of mice. That partially cured the hearing loss in the mouse model of Usher. There is another group that tried a gene therapy study looking at connexin mutations, a really common form of acquired deafness, and they have partial hearing preservation in a mouse model of connexin deafness. So the studies are starting to accumulate, now. It is a very exciting time for gene therapy for hearing loss, really.

Has any gene therapy in the ear ever been done in humans?
The Novartis study has just been started. The first patient was injected at the University of Kansas I believe about two or three months ago. Again, that is part of a FDA phase 1 trial - it's only a safety study. A very small amount of virus was injected and the data on that's not going to be released for a while, yet.

Will there be a forthcoming publication on your Usher III research?
Yes. In fact, Kumar and our group are working on a joint publication to try to get this work out. We're going to present the data at the winter meeting of the Association for Research in Otolaryngology which is one of the premier auditory research meetings in the world. At the same time we are going to be putting together all of our data combined for publication in a high impact scientific journal.

Is there anything that you think we haven't covered that people would like to hear?
This is the first great step in the treatment of Usher III because what we're doing in the ear can also theoretically be applied in the eye. Like I said, if we can intervene before the onset of the hearing loss we could make a huge difference in these patients' lives. And even if it doesn't work, we still have cochlear implants as a backup. So we have a good treatment [cochlear implant] - we're working on a better treatment. There's no question that your natural hearing is still better than a cochlear implant, so it's worth continuing to try to restore normal hearing with these research studies.

More research highlights from this year…

Our team met last month and reported some exciting progress. Proof of concept in hearing rescue has been demonstrated in both gene therapy and small molecule and, with preliminary data, rescue of vision has been shown using gene therapy. Our researchers are continuing to follow up on their studies to further support their findings. They are also focused on drafting articles for publication and preparing for presentation of their work at industry conferences.

At Cleveland's Case Western Reserve University, important work was completed and critical milestones lie ahead:

· Kumar Alagramam in the Department of Otolaryngology at Case piggy-backed his Usher III research on his National Institutes of Health funded work. The transgenic mouse model he produced in the latter project was the basis for a successful proof of concept testing of our small molecule compound. Mice were treated for 15 days and, when tested approximately 30 days after the first treatment, the treated mice showed statistically significant improvements in hearing compared to the untreated (control) animals. He repeated his experiment treating the mice at a younger age with gradually increasing doses of the compound. This test showed an even more dramatic decrease in hearing loss. It is important to note that virtually ALL mice tested showed decreased hearing loss as compared to the untreated animals.

· Yoshikazu Imanishi at Case Western has completed an extensive study of how the small molecule compounds that have been developed over the last eight years at Case and a contract laboratory interact with the Clarin1 protein. Understanding how these molecules work will help us develop the compounds as therapeutics. It may 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.

· Dr. Imanishi also continued work he had previously started on trying to create a mouse with an eye dysfunction similar to Usher. Demonstrating a loss of vision beyond the initial few months of life has proven to be more challenging largely due to challenges with the mouse as a model for the visual phenotype.

· Using a specially developed frog model, Dr. Imanishi showed that the small molecule treatment can increase levels of Clarin1 protein in the retina, further supporting the theory that mice are not an ideal model to get a visual phenotype and do subsequent tests to test vision therapies.

· In his collaboration with the Hauswirth lab at the University of Florida, Dr. Imanishi identified an antibody that detects Clarin1 introduced by AAV (adeno associated vector) in the photoreceptors and retinal pigment epithelium (RPE) cells.

· Our team of researchers at Case (Kumar Alagramam, Yoshikazu Imanishi and Krystof Palczewski) are collaborating on a publication that will describe the ground-breaking research and results they have achieved over the last several years. They plan to submit the work to a major scientific journal next year.

· Dr. Alagramam is also collaborating with Dr. Lustig at Columbia (formerly UCSF) to write an article describing his support of the successful gene therapy treatment aimed at hearing rescue in a mouse model. You can read more about this in the spotlight on Dr. Lustig, below.

As mentioned above, Bill Hauswirth's lab at the University of Florida continues to pursue gene therapy treatments for Usher III in the eye. Great progress was made in 2014 toward this end including the following:

- Several AAV vectors were created to test gene therapy and Clarin1 localization (tracking) experiments in the ear (by the Lustig lab) and the eye (Hauswirth lab). The development of the vectors incorporated findings from the Alagramam NIH research which increased the chance of success in the mouse models.

- Intravitreal injection of the gene therapy vector showed a trend toward improved vision at three months of age and became statistically significant at five months of age. Additional animals have been treated and results are pending.

- Dr. Hauswirth's lab continues its work to develop mice with Usher-like visual symptoms by looking at changes in arrestin transport following light exposure. The results are promising but additional mice need to be tested to verify the result.

Last but, certainly, not least… Our newest researcher Dr. Lawrence Lustig and his lab at the University of California San Francisco tested mice obtained from the Alagramam lab with vectors from the University of Florida with gene therapy injections in the ear. There was a clear treatment effect in 40% of mice showing significant (near normal audio brainstem response or ABR in some animals) and long term

preservation of hearing compared to untreated animals. As Dr. Lustig elaborates in our interview with him earlier in this newsletter, while these results are promising, additional studies will need to be done in order to validate the results.

Many of the results from Usher III Initiative researchers are promising. Perhaps the most exciting observation we've made has been how well the research teams are working together and the fact that their collaborations are clearly helping the individual labs achieve better results on a shorter timetable! This is so important for Usher patients who are hoping for treatments as quickly as possible.

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.

Ways to get involved!

The Usher III Initiative's top priority is to develop a treatment for patients with Usher III. Because Usher III is an orphan disease that does not affect a large population, it is important that each and every patient join our efforts to prepare for clinical trials. We hope that gathering patient information will help all patients gain access to treatments more quickly.

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 and rehabilitation centers. The more data in the database, the more powerful it is in terms of providing valuable information to researchers, funders and government agencies! The database is compatible with JAWS and other readers. It is currently available in English, Spanish, Hebrew, and Dutch. German, Portuguese, French, Swedish versions are in development.

2. **GET A BLOODTEST (GENOTYPING)**. 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, Iowa City
Bill Kimberling, Ph.D.
https://www.carverlab.org/projectusher/instructions

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

Harvard Medical School and Partners Healthcare, Cambridge and Boston
Heidi Rehm, Ph.D., FACMG
(617) 768-8500
http://pcpgm.partners.org/

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.

Have you read Rebecca Alexander's book?

The positive reviews continue to roll in on Rebecca's book ***Not Fade Away*** about her experiences with Usher Syndrome, Type III! If you haven't picked up your copy, click here!

Check out this publication by our featured researcher, Larry Lustig!

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

USHER III INITIATIVE

Looking Ahead…

- **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.
- **Twitter**…we can also be followed on Twitter! Our handle is @UsherIII (https://twitter.com/UsherIII)
- **Support us through your Amazon purchases…** If you shop on Amazon, you can designate the Usher III Initiative as your charity of choice and Amazon will donate a portion of all your eligible purchases to the Usher III Initiative! Click through to smile.amazon.com and follow the steps to designate us as your preferred charity and DON'T FORGET to order through AmazonSmile, in the future!

Contact Us…

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

By Telephone…(312) 896-2509
By Email…info@usheriii.org