STEP UP 4 AHC

FUNDING THE AAV PROJECT AND AHC RELATED RESEARCH

AHC Foundation Newsletter December 2019

SEASON GREETINGS FROM OUR PRESIDENT – Josh Marszalek

As the year draws to a close, the Board of Directors and I extend our best wishes to you and your family for a joyful holiday season and a very Happy New Year.

At this festive time, we find ourselves reflecting on the past and those who have helped shape our community. The AHCF was here when few people had heard of AHC and even fewer doctors knew about it. Through the years, we have worked every day to fund research while meeting the needs of those affected with AHC. We also provided information and support to family members, letting them know they are not alone.

Thank you for giving us the opportunity to do what we have a passion for by supporting the foundation in numerous ways. It's been an exciting and productive year for us, and we hope that 2019 has been kind to you as well.

We look forward to exciting opportunities in 2020 and meeting with many of you at the AHCF Family Meeting. We could not do all that we do without you. Thank you and Happy New Year!

IMPORTANT AAV PROJECT UPDATE

News About the Research You are Funding

We are pleased to share our latest progress on the AAV gene therapy project. Keeping with our space travel analogy, we are excited to announce that we now have astronauts (mice) for our rocket-ship! We are loading the rocket-ship with supplies and anticipate a launch in January 2020 to start behavior tests to see if we can get a "rescue" of a mouse with AHC using our vectors.

As a reminder, since June 2018, AHC Foundation, CureAHC and Hope for Annabel have been collaborating on a gene therapy effort using Adeno Associated Virus (AAV) as a system to deliver functioning ATP1A3 to compensate for the mutated ATP1A3 associated with AHC. This project will require many phases, or rocket-ship flights, with several steps in each phase/flight to hopefully get to a clinical trial by 2022. We are just in the first phase of the AAV Project where we are developing a viral vector and testing its effects in mice.

In our last update in June 2019, we discussed how scientists around the world collaborated to test and improve our vectors, and that we filed patents with the help of law firm Cozen O'Conner to

AHCF
Serving the International AHC community since 1993

AHCF Newsletter

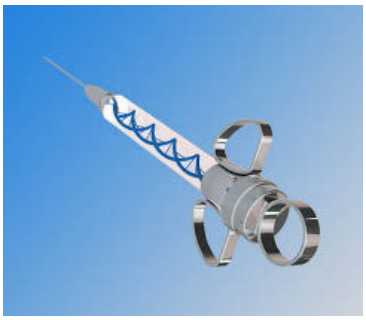
Sharing information for advocates, caregivers, professionals and families.

Thank you to everyone who helped raise funds during the months of November & December.

You are doing the most important work for AHC research and your efforts are greatly appreciated.

THANKS!

AAV Update Continued from Page 1



protect the science and try to keep costs of treatment as low as possible for patients and parents. We also shared that we needed to do additional "quality control" testing on bio-distribution and potency of our viral vectors to make sure they are as effective as possible before we test them in mice with AHC.

We have astronauts, and more coming by the day: After some initial problems trying to breed and maintain a colony of mice with AHC, we made some changes to our "astronaut" training program and are now incredibly excited to share that we have three (3) colonies thriving at two different labs. While these colonies will provide us with enough mice for our behavior experiments, the mice are also "open source" meaning that we can share them with other scientists to help promote further research into AHC and treatment options. All of us on the committee will never look at mice the same way again (they are heroes too)!

We have finalized our supply list and are ready for our first launch: After repeating tests on our vectors and making modifications, we have a revised batch of vectors ready to be used for this rocket-ship launch. In early 2020, we will inject these vectors into mice with AHC and then conduct behavior tests to see if the symptoms of the mice have improved. Depending upon results, we will know whether the vectors delivering functional ATP1A3 have helped the mice with AHC compensate for their poorly functioning mutated ATP1A3.

We are sharing our supply list with other space travel programs: In order to best demonstrate the effectiveness of our vectors, we are sharing them with other scientists who can test them in other ways. So, in addition to our work collecting data about the vector's effects on our mice with AHC, by collaborating with other scientists we may be able to show how the vectors also impact human stem cell lines. Drs. Kevin Ess (Vanderbilt) and Al George (Northwestern) have agreed to test our vectors on their collection of induced pluripotent stem cells of patients with AHC. This data could be tremendously useful as we move closer to a clinical trial because it will demonstrate impact on human cells.

We are exploring other forms of space travel: While we are very hopeful that our AAV gene therapy delivering functioning ATP1A3 will be effective, we are not content putting all of your fundraising efforts into one rocket-ship. We are working with Dr. Steven Gray (UT Southwestern) to produce and explore "knockdown options" using sequences of RNA and "ASOs" to interfere with, silence and prevent protein expression in specific cells. We were also excited to read in a recent article in the journal Nature about some advances in CRISPR using a technique called "prime editing." Both these knockdown options and CRISPR prime editing are other forms of "space travel" that may lead to more personal and effective treatment options for AHC in the future.

Another exciting type of "space travel" is a possible genome project where the foundations may be able to help cover the costs for genome testing for any patient who has not yet undergone this testing. We are working to find a lab and scientists to collaborate with us to gather an open-access, anonymized genome database of all our AHC and ATP1A3 patients. By doing whole

THANKS

The AHCF Board of Directors extend our thanks and appreciation to Rik Greenwood for his service to the foundation.

Rik provided helpful insight and perspective to many aspects of our work.

We wish him and his family all the best.

Thank you for your service.

AHCF 2019 Directors:

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genome testing, we hope this will be a catalyst for more research and to help doctors, scientists and families by identifying related diseases, a second causative gene, and modifier genes as potential therapeutic targets. In addition, a genome database may help us develop more precise therapies for our AHC patients and accelerate natural history studies for clinical trials. More details on this project coming soon.

Keep supporting our AAV gene therapy mission: As a community, we need to continue to raise money so that we can fund and control the development of a possible effective AAV gene therapy on our terms to try to ensure access for all families. The more money we raise as a community, the more leverage we have in negotiating terms as we move towards clinical trial by 2022.

Families and organizations wanting to support the AAV Project should feel comfortable directing fundraising efforts to one, two or all three of the foundations: AHC Foundation, CureAHC or Hope for Annabel.

For questions about the AAV Project or specific fundraising efforts,
please contact Josh Marszalek (Joshua@ahckids.org)

PUBLISHED RESEARCH SHEDS LIGHT ON AHC

Three New Papers Offer Important Insights

This fall, a lot of research was published on AHC and ATP1A3-related disorders. Three articles are highlighted here to summarize some of the important discoveries covered in the papers.

In the December issue of *Neurological Sciences*, an article was published titled, **"Epilepsy and Brain Channelopathies from Infancy to Adulthood."**

A group of Italian scientists provided an overview of genetic brain channelopathies associated with epilepsy which included; migraine, episodic ataxia, alternating hemiplegia, as well as chronic phenotypes, such as spinocerebellar ataxias, intellectual disability and autism spectrum disorder.

The paper highlighted that recognizing the prominent phenotypical traits of brain channelopathies is essential to perform appropriate diagnostic investigations and to provide better care not only in the pediatric setting but also for adult patients and their caregivers.

Recognizing the different clinical characteristics is important because it may prompt the clinician to suspect specific syndromes and to possibly establish tailored treatments.

In *Pediatric Neurology,* an article was published called, **"Management of Alternating Hemiplegia of Childhood: A Review."** The paper recognized that with rapid advancement in the understanding this disease, the treatment paradigm of alternating hemiplegia of childhood may significantly alter over the next decade. However, they do provide guidance on how to manage the burden of neuromorbidities such as epilepsy; attention-deficit/hyperactivity disorder; behavioral difficulties; motor, cognitive, adaptive, and learning impairment; ataxia; movement disorders; and migraine.

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PUBLISHED RESEARCH continued

A December paper in *The Neurobiology of Disease*, was published by several researchers well known to our community, as well as an AHCF Medical Advisory Board member. The title of the paper is, **"Factors in the Disease Severity of ATP1A3 Mutations: Impairment, Misfolding, and Allele Competition."**

The paper found two cell biological complications. First, there was impaired trafficking of αβ complex, as well as changes in cell morphology, for two mutations that produced microcephaly or regions of brain atrophy in patients. Second, there was competition between exogenous mutant ATP1A3 (α3) and endogenous ATP1A1 (α1) so that their sum was constant.

This predicts that in patients, the ratio of normal to mutant ATP1A3 proteins will vary when misfolding occurs. At the two extremes, the results suggest that a heterozygous mutation that only impairs Na,K-ATPase activity will produce relatively mild disease, while one that activates the unfolded protein response could produce severe disease and may result in death of neurons independently of ion pump inactivation.

A copy of this paper is available for free online and can be found at the following link:

https://www.sciencedirect.com/science/article/pii/S0969996119302451?via%3Dihub

ENDING THE YEAR STRONG

Working to End AHC Together

Over the last 18 months, we've been working with CureAHC and Hope for Annabel to create something that doesn't exist. A treatment for AHC. Every aspect of the project has been a collaborative effort. Even some of the fundraising.

Collaborative fundraising—is now gaining popularity. And the opportunities are real: Fundraising together, charities can reach goals

and create the sort of impact we might never be able to achieve by ourselves. Through collaboration, we can expose our organizations to new potential donors and supporters, and experience heightened public awareness around our mission and work. Meanwhile, donors are looking for organizations to work together and bring in more of the community so that their support can have more far-reaching impact.

The collaboration isn't just within the U.S. Family foundations from around the world are joining the AAV project. Together, our AHC family is making great strides to realizing our One Mission: End AHC.

WATCH FOR INFORMATION ON REGISTERING FOR THE FAMILY MEETING IN THE NEW YEAR!

New programming and new opportunities to learn about AHC for all AHC families.