STEP UP 4 AHC

FOUR PROJECTS FOR ALTERNATING HEMIPLEGIA OF CHILDHOOD

AHC Foundation Newsletter

November 2018

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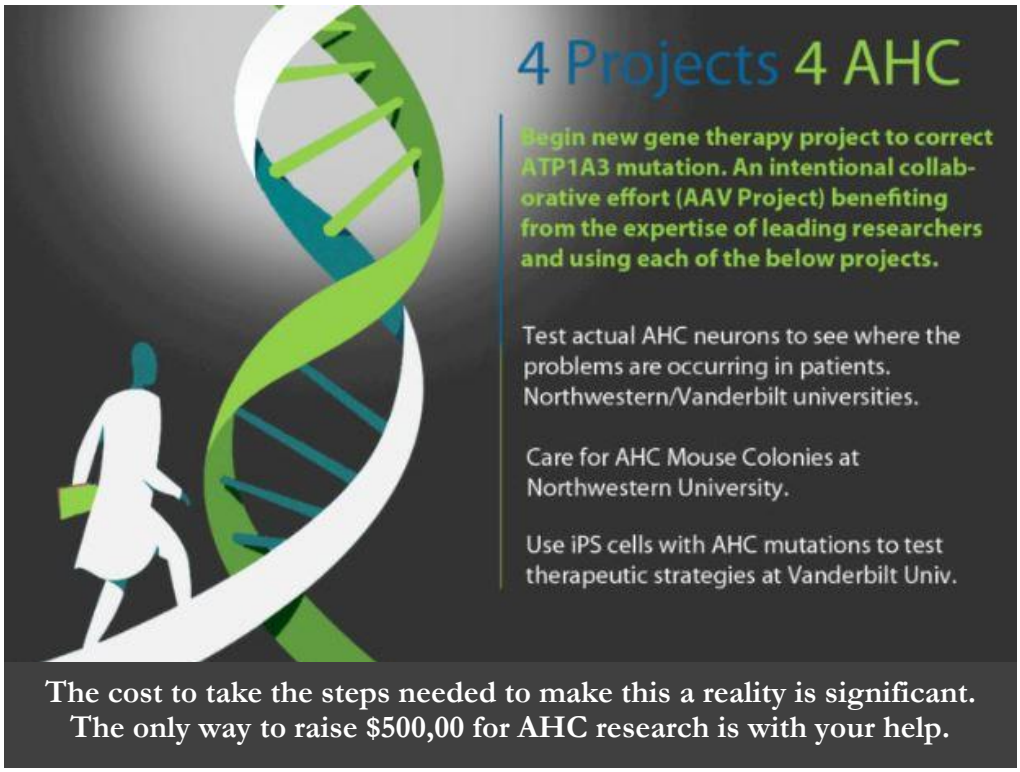
THE CAMPAIGN TO FUND THE TREATMENT
YOU'VE BEEN WAITING FOR HAS STARTED !!!

The **biggest year end fundraising campaign** ever undertaken by AHCF started on November 1st. As we prepare to make the largest investment ever made in AHC research in 2019 you'll be amazed at what is now within reach for our AHC community.

The campaign is called "Step Up 4 AHC" because it will build around on-going research and initiate new research on gene therapy waiting to begin in April 2019. Here are the four projects being funded by the AHCF in 2019.



The cost to take the steps needed to make this a reality is significant. The only way to raise $500,00 for AHC research is with your help.

Funding the AAV Project will take the effort of the entire AHC community. Now is the time to work with the **AHCF** and make this a reality for all families living with AHC. Let's not wait another minute for this treatment. **The time to end AHC is NOW!**

To comment on the newsletter contact: Vicky Platt at vicky@ahckids.org

AHCF Serving the International AHC community since 1993

It is time to join the movement.

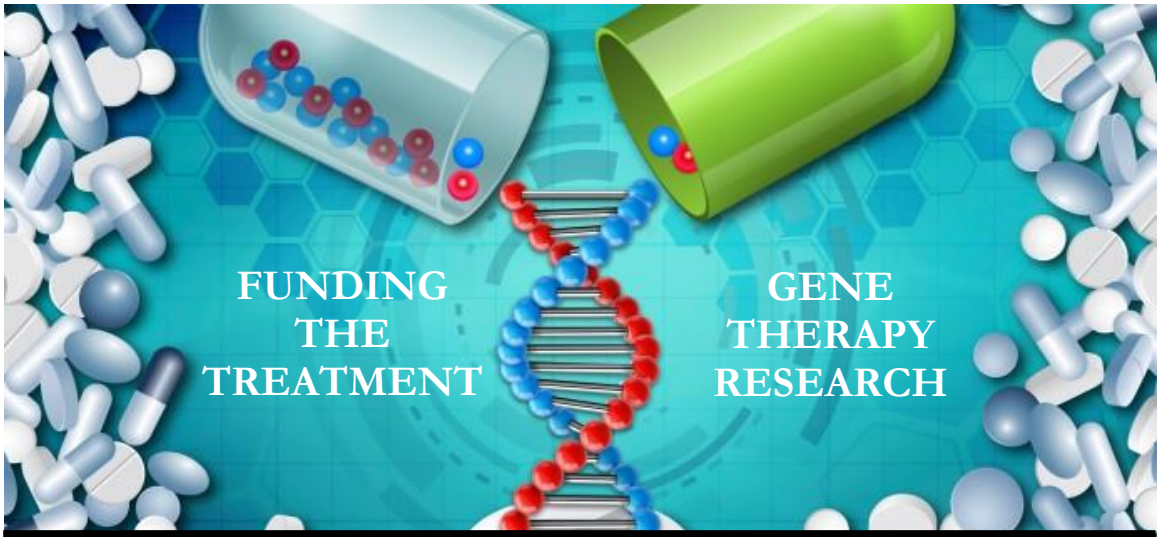
●

Be part of the team making the AAV Project a reality.

●

Contact Lynn Egan for more info on how you can help.

lynn@ahckids.org



The Step Up 4 AHC Campaign needs $500,000 to move forward. Here is why it is so important.

- **Gene Therapy Works** - Put simply, gene therapy works by changing the genetic information of a population of cells in a way that alleviates or combats the cause or symptoms of a disease.
- **Risk is Reduced -** Put simply, gene therapy uses viral vectors to reduce the risk of adverse effects, and each vector is rigorously tested in cells and animals before considered for human use.
- **It is Working for Other Rare Diseases** - Put simply, gene therapy is the focus of current research for SMA where they are also working on issues similar to AHC, like protecting motor neurons.
- **Researchers Think This will Work for AHC** - Gene therapy for AHC presents some challenges, but a team of the top scientists in this field are already assembled to begin addressing these challenges.
- **Collaboration is in Place –** AHCF, CureAHC and Hope for Annabel foundations are currently working together to make this project a reality for the AHC community.

LOOKING FOR HELP UNDERSTANDING THE AAV PROJECT?

We have numerous resources to help you along the way. How about starting with a webinar which took place earlier this month.

Go to www.StepUp4ahc.org and under the AHC Campaign Information button you will find a recording of the webinar with Simon Frost available for you to view on your own time.

It is a great introduction to the AAV Project and a great tool to share with your family and friends.

AHCF Donated over $3 million to fund AHC research prior to the AAV Project

DONATE

To verify the financial strength of our foundation, check out our status with GuideStar or Great NonProfits.

Holiday Shopping and AmazonSmile Go Together Like Peas and Carrots

amazonsmile
You Shop. Amazon Gives.

How One Mom Donated over $50 without Spending a Dime

One AHC mom was happy to share with us that this year, before she began her holiday shopping, she helped raise over $50 for the foundation.
And, she did it without spending a dime of her own money. She did it by using AmazonSmile.

As part of her responsibilities at work, she orders books for the firm all year long. By using AmazonSmile for those orders, the donation coming to the AHCF was just over $50 this year. It turned out to be a great way to help fund research while doing her job.

Do you still have holiday shopping to do?
If you do, you too can help raise money for the AHC Foundation's Year End Campaign,

Step Up 4 AHC.

Simply switch to AmazonSmile and the Amazon Foundation will donate 0.5% of the purchase price of eligible products to the AHCF.

This small switch can help raise money for AHC all year long and will cost you nothing extra.

Setting up AHCF as your charity of choice will make sure the funds come to us. Thank you for helping achieve the mission of Ending AHC!

amazonsmile
You shop. Amazon gives.

DONATE

AHCF Fun Fact

The AHCF has our GuideStar Silver Seal of Transparency which indicates that we have provided GuideStar key information in our Nonprofit Profile. By providing the information, we allow potential donors and funders to make educated decisions about the work we do. Check it out.

The AAV Project came about because of the hard work of AHC parents.
The AAV Project has the potential to change the future of all people with AHC.
The AAV Project's Success is Your Success.
The End of AHC will only come about with YOU!

HERE IS HOW YOU CAN HELP

DONATE

Contribute financially to the campaign for Gene Therapy and 3 other projects for AHC. Get creative, if you have a big donation, maybe make a matching challenge the community!

RAISE DONATIONS

Raising money in your networks adds up to more than your contribution alone. Just asking 10 of your closest friends for $50 makes a quick $500 for your AHC hero. Imagine if you asked 10 more of your not-so-close friends to donate the value of a lunch!

Whether it be via social media and Facebook, through the mail, or via email, we have the tools for you to do it easily! Discuss your ideas with us, and we can make your ideas happen.

AHC COMMUNITY CONNECTIONS

Dr. Al George Reports from the Symposium

The 7th Annual ATP1A3 in Disease Symposium took place on October 13-14, 2018 at the Feinberg School of Medicine at Northwestern University in Chicago, Illinois.

Experts on Na+/K+-ATPase and ATP1A3-related diseases from all over the world were attended this scientific meeting with a very impressive program.

The following summary of the meeting was kindly put together by Dr. Alfred L. George so the AHCF could share it with our parents. It is long, but an amazing summation of the wonderful work being done around the world to help End AHC. We sincerely thank Dr. George for his hard work and professionalism in tending to all aspects of this symposium.

The conference attracted approximately 90 speakers, discussion leaders, trainees, families, representatives of international foundations, as well as thought leaders from NIH and industry. A major goal of this conference was to integrate more young investigators into the program, and to highlight aspects of ATP1A3-related disorders that have not received much attention at prior meetings.

The conference was organized around 5 themes: Basic Science of ATP1A3, Non-motor Symptoms, Clinical Features and Treatment of Dystonia, Epilepsy in ATP1A3-related Diseases, and New Therapeutic Approaches. **Continued on Page 5…**

To volunteer with the AHCF contact Lynn Egan at: lynn@ahckids.org

Check out our website

www.ahckids.org

SHARE AHC INFO

If you know of friends, family teachers, or therapists who would benefit from our newsletter, share this issue with them & ask them to join our mailing list.

AHC COMMUNITY CONNECTIONS

Dr. Al George Reports Continued…

In addition to the invited speakers, there was a poster session featuring 22 presentations from which 7 were selected to give short oral presentations during the conference. There were two keynote addresses given by Dr. Chris Gomez (Professor of Neurology, University of Chicago) and Dr. Joan Anzia (Professor of Psychiatry, Northwestern). Dr. Gomez explained how his laboratory investigated spinocerebellar ataxia, a rare neurological disorder, from basic discovery to development of novel therapeutic approaches. Dr. Anzia talked about physician and caregiver burnout as a serious consequence of managing chronic diseases.

We also had guest lectures by Dr. Nina Schor (Deputy Director of the National Institute of Neurological Diseases and Stroke) and Dr. Jonathan Mink (President, Child Neurology Society). The conference was highly successful, and attendees left with a sense of significant progress in the field. This report summarizes the main points discussed at the conference without disclosing confidential information communicated by the presenters. The report is organized by the 5 main session themes.

Basic Science of ATP1A3

A core group of speakers and several of the poster presenters emphasized progress in determining the molecular and cellular mechanisms underlying ATP1A3-related disorders. Dr. Kathleen Sweadner and her colleague Dr. Elena Arystarkhova shared a new idea to explain the dominant effect of heterozygous mutations that involves impaired biosynthesis and trafficking of the ATP1A3 protein. These newly recognized mechanisms for ATP1A3-related disorders may inspire new therapeutic uses of drugs that can restore normal protein folding. Later in the conference, Dr. Sweadner explained how certain ATP1A3 mutations have been mis-identified by genetic testing laboratories that use an alternative reference sequence for the gene.

Additional mechanistic insight into the dysfunction of ATP1A3 mutations were provided by Drs. Bente Vilsen and Miguel Holmgren. Dr. Holmgren and his postdoctoral trainee (Cristina Moreno) from NIH presented results from their in-depth investigations of the D923N mutation, which interferes with binding of sodium ions (Na+) to a specific site in the protein. Similarly, Dr. Vilsen focused her presentation on mutations that affect Na+ binding. She also presented new information about the CAPOS mutation (E818K) that suggested that the mutation disrupts Na+ binding as well, and has other features that are not consistent with a gain-of-function, which was proposed initially. The last presentation in this session by Dr. Keiko Ikeda discussed the features of ATP1A3 knock-out mice, and emphasized a functional interaction between ATP1A3 and a glutamate transporter that may be relevant to certain disease phenotypes.

Non-motor Symptoms

This session emphasized neuropsychiatric symptoms associated with ATP1A3-related disorders. Dr. Hendrik Rosewich led the session with a review of psychiatric and cognitive features of ATP1A3 diseases. He reported that impaired cognitive function is common in AHC, but less prominent in RDP and CAPOS. In RDP, cognitive impairment is more severe in patients with motor symptoms. Psychiatric symptoms are less well described in ATP1A3-related diseases, and there is a need to systematically collect these data. Mood disorders occur in approximately 20% of patients.

Do you have questions about AHC? Are you looking for people who understand life with AHC? We're here to help. www.ahckids.org

The AHCF Board of Directors is pleased to announce that Cate Cohen has been elected to serve the foundation for a three year term beginning this month. Please join us in welcoming Cate back to the board.

AHCF 2018 Directors:

Gene Andrasco
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Mario Merida
Carol Presunka
Josh Marszalek
Meredith Schalick

AHC COMMUNITY CONNECTIONS

Dr. Al George Reports Continued…

He gave a preliminary report on a pilot study to assess social, cognitive, and practical competencies among patients with ATP1A3 mutations.

Dr. Diane Doummar reported discussed four French patients with novel ATP1A3 mutations that had epileptic encephalopathy without hemiplegic attacks. All subjects shared features of hypotonia, seizures, intellectual disability, and early age at onset of symptoms (less than 6 weeks of age). She suggested that epileptic encephalopathy should be considered part of the clinical spectrum of ATP1A3-related disorders.

The remaining presentations of this session focused on psychiatric symptoms associated with ATP1A3 mutations. Dr. Catherine Brownstein presented a case of congenital schizophrenia associated with a novel ATP1A3 mutation. This was followed by two young investigator presentations (Richard Smith, Christopher Thompson) who described cellular and molecular mechanisms for the dysfunction of ATP1A3 in this case. These findings add to the expanding clinical spectrum of ATP1A3 disorders. The last presentation by Dr. Thomas Holm described his hypothesis that many features observed in the D801Y mutant mouse model of ATP1A3 disease are shared with schizophrenia, and he showed preliminary data in which a novel compound could reverse some of these features.

Clinical Symptoms and Treatment of Dystonia

In this session, we heard an update on a systematic effort to delineate the clinical features of RDP given by Dr. Ihtsham Haq, and a presentation on the use of deep brain stimulation to treat Parkinson disease by Dr. Harrison Walker. Dr. Haq emphasized how the features of RDP have become clearer with review of data from a 10-year follow up study of 50 cases. For example, the onset of symptoms was not 'rapid' in all cases. Other 'typical' features of RDP may not be as uniform among patients as previously thought. He concluded that there should be a lower threshold for performing genetic testing for ATP1A3 mutations in cases that have some, but not all, features of RDP.

Dr. Walker discussed how deep brain stimulation can result in dramatic improvements in adults with Parkinson disease. There has been limited experience using this therapy in RDP, and the results were not encouraging. He emphasized the need for a more systematic study to determine if deep brain stimulation can help these patients.

Two trainees complemented this session with their presentations on the use of patient-derived induced pluripotent stem cell technology to study ATP1A3 mutations (John Snow), and illustrations of novel ATP1A3 mutations associated with atypical clinical features (Linh Tran).

Epilepsy in ATP1A3 Diseases

This session featured two speakers (Erin Heinzen, Mohamed Mikati) who discussed different aspects of seizure disorders associated with ATP1A3 mutation. Dr. Heinzen focused on genetic epilepsy disorders and use of exome sequencing to discover novel genes. She provided an update on efforts to find other genes associated with AHC-like disorders. Dr. Mikati reviewed his approach to managing epilepsy in the setting of ATP1A3 mutations, and reported on the clinical features of seizures in these patients. Seizures are common among AHC patients (60%) and some exhibit seizures before the onset of motor symptoms of AHC. He concluded by emphasizing the importance of treating seizures, sleep disturbances and neuropsychiatric symptoms associated with ATP1A3 mutations.

Continued on page 7…

AHC COMMUNITY CONNECTIONS

Dr. Al George Reports Continued…

Dr. Nina Schor highlighted the importance of studying rare neurological disorders from her perspective as Deputy Director of NINDS. She emphasized that in child neurology clinics, rare diseases collectively are not rare. The NIH deems rare disease research important for many reasons.

Dr. Simona Balestrini gave a brief update on their study of electrocardiographic (ECG) abnormalities in patients with ATP1A3 mutations. Their study now has 112 participants, mostly with AHC (97). They have largely confirmed their previous published study, but had interesting follow-up data for some patients who required pacemakers because of abnormal heart rhythms.

New Therapeutic Approaches

In the last session of the conference, attendees were energized by talks about future therapeutic opportunities for ATP1A3-related diseases. The session began with a discussion of imaging biomarkers given by Dr. Christopher Whitlow. His ongoing study using MRI to image the brains of RDP patients has provide insights into the brain regions most affected by the disease, along with new correlations between brain structure and clinical features. Biomarkers are important for following the clinical course of the disease, and will help evaluate the success of therapies.

Alan Lewis presented his work investigating the therapeutic benefits of transdermal nicotine to control challenging behaviors in children with autism and other neurodevelopmental disorders. In an exploratory trail of adults with autism, transdermal nicotine improved irritability, suppressed aggressive behaviors, and improved sleep in many, but not all, subjects. This therapy may have value in some older patients with ATP1A3 mutation who exhibit such behaviors.

In the last two talks of the meeting, Dr. Steven Gray and Dr. Barry Ticho presented two distinct approaches for gene therapy of rare genetic neurological disorders. Dr. Gray discussed use of viral gene delivery to the brain through the spinal fluid (intrathecal delivery). He is developing an adeno-associated virus (AAV) to deliver ATP1A3 to mouse brain, with the short term goal of testing the efficiency of delivery. There are many AAV gene therapy trails ongoing for various genetic conditions, and ATP1A3-related diseases may one day benefit from this therapeutic strategy.

Dr. Ticho from Stoke Therapeutics introduced a strategy to boost expression of proteins expressed in the brain. The technology, called TANGO, exploits a natural form of 'poison' exon that can be suppressed to force cells to make more of a targeted protein. Their company is working on a therapy for Dravet Syndrome, but has begun exploring ATP1A3 as a potential therapeutic target.