

## **Cure AP-4 Research Conference: 11/01/2019**

*Graciously hosted by BCH Translational Neuroscience Center*

- Meeting location:** Center for Life Sciences  
3 Blackfan Circle  
12th floor conference room #12007  
Boston, MA 02115
- Meeting Time:** November 1<sup>st</sup>, 12pm to 4pm  
*Lunch will be provided!!*
- Contact phone:** Jessica Kim, Administrative Assistant for Translational Neuroscience Center  
(617) 919-6258
- Parking:** Corner of Longwood Avenue and Blackfan Circle (Boston Children's Hospital patient garage)
- Zoom Meeting:** Join from your computer or mobile device:  
<https://bostonchildrens.zoom.us/j/492473966>
- Or dial in from your telephone:  
Internally: x28882  
Externally: 646-558-8656 (Primary)  
408-638-0968 (If you are unable to dial into the primary)
- Or iPhone one-tap:  
+16465588656,,492473966# or +14086380968,,492473966#
- EWS link: <https://zoom.us/jc/492473966/join>
- Meeting ID: 492 473 966

### **Introduction:**

Thank you for participating in our third annual Research Conference! Earlier this year, our non-profit mission was expanded from seeking treatment options for SPG47 to include three additional closely related Hereditary Spastic Paraplegia sub-types: SPG50, SPG51 and SPG52. Together, these four sub-types comprise the AP-4 –associated HSPs, hence our newly re-branded organization: “Cure AP-4”.

During previous face-to-face meetings of CureSPG47 families and medical advisors, various possibilities for research and treatment have been discussed – including tradeoffs and probability of success. A consensus was reached early on that gene therapy offered the greatest hope for meaningful treatment during the lifespan of SPG47 patients identified at the time. Soon after that initial meeting, CureSPG47 entered into a research agreement with the University of Sheffield. Principal Investigator Dr. Mimoun Azzouz, who is now more than two years into the project, will be presenting the latest updates on progress with the project and a roadmap towards the first human clinical trials. A gene therapy proof of concept for SPG50 is currently underway at University of Texas Southwestern under the direction of Dr. Steven Gray, and Requests for Proposals for SPG51 and SPG52 are being processed currently.

Late in 2017, CureSPG47 was able to enter into a second research agreement, this time with Boston Children’s Hospital. Under leadership of Principal Investigator Dr. Darius Ebrahimi-Fakhari, a drug-screening on patient-derived re-programmed iPSC-derived neurons is now underway. Also under leadership of Dr. Ebrahimi-Fakhari, the first ever International AP-4 Natural History Study and Patient Registry are underway. A great deal has been learned about AP-4 HSP, and our patient numbers have grown dramatically thanks to these critical efforts. Darius will be presenting the latest findings and progress on both efforts at this Research Conference as well.

The purpose of this third face-to-face meeting is to:

- Recap what has been learned about AP-4 HSP
- Discuss progress in the ongoing research projects
- Discuss applicability of successes with other rare diseases
- Explore the most expedient options for obtaining regulatory approval for future human clinical trials

On behalf of the families affected by AP-4-HSP, we truly appreciate your willingness to participate in this effort. We are truly blessed that so many impressive people are involved in the effort to understand and treat these devastating disorders!

#### **Cure SPG47 Board of Directors:**



Kira Dies, ScM, CGC: *Co-director of Clinical Research and Regulatory Affairs Service, Translational Neuroscience Center, Boston Children's Hospital.* Kira is a licensed genetic counselor at BCH. She has a deep understanding of the underlying genetics of neurodegenerative diseases like HSP. She manages multi-site clinical trials for neurogenetic conditions including tuberous sclerosis complex, Rett syndrome, and PTEN hamartoma syndrome.



Kevin Duffy: *Head Golf Professional, Riverton Country Club.* Kevin is Molly Duffy's father. He has been working in the golf industry for more than 15 years and is currently responsible for leading the golf operation at Riverton CC on both an operational and strategic level. His areas of expertise include marketing, relationship management, customer service, team building and coaching.



Chris Edwards: *Chief Executive Officer, Alternative Therapies Group*. Chris is Robbie Edwards' father. He has founded a series of startup companies during his career. He has extensive experience in building/managing teams with diverse skills sets, and with navigating complex governmental regulations and problem solving.



Erika M. Gill, MBA: *VP, Rare Blood Disorders Patient Solutions, Sanofi Genzyme*. Erika has over 20 years' experience in health care and biotech, leading several cross-functional areas including program management, patient services and education, marketing and health care administration across multiple disease areas.

#### **Cure AP-4 Network of Medical and Scientific Advisors:**



Dr. Mimoun Azzouz: *Chair of Translational Neuroscience, ERC Advanced Investigator, Director of Research and Innovation, University of Sheffield*. Dr. Azzouz has a long-standing interest in developing gene therapy approaches for neurodegenerative diseases. His team utilizes viral-based gene transfer systems both for research and gene therapy applications.



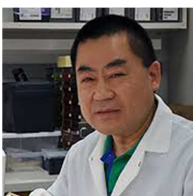
James T. Bennett, MD, PhD: *Pediatric Geneticist, Seattle Children's Hospital Genetics Care Team, Associate Editor American Journal of Medical Genetics*. Dr. Bennett is board certified in Clinical Molecular Genetics. He has initiated a project of collecting and reporting pertinent medical information for known SPG47 patients.



Dr. Craig Blackstone: *Senior Investigator, Cell Biology Section, National Institute of Neurological Disorders and Stroke, NIH*. Dr. Blackstone's laboratory investigates the cellular and molecular mechanisms underlying hereditary movement disorders. Craig is one of the most prominent HSP researchers in the world.



Georg Borner, PhD: *Max Planck Institute of Biochemistry Group Leader*. Dr. Borner is investigating the molecular details of AP-4 deficiency syndrome. His lab recently uncovered a direct link between AP-4 mediated transport and the spatial control of autophagy, via sorting of the core autophagy machinery protein ATG9A, providing a potential mechanism for AP-4 pathology.



Xin Chen, PhD: *Instructor, UT Southwestern Medical Center*. Dr. Chen has been successfully generating favorable efficacy and safety data using AAV9 gene therapy to treat both AGU and CLN7 knockout mouse models in Dr. Steven Gray's laboratory. Both of these projects are now at the stage of IND enabling. He is excited to be working on a gene therapy proof-of-concept for

SPG50 under direction of Dr. Gray.



Dr. Basil Darras: Associate Neurologist-in-Chief, Chief-Division of Clinical Neurology, Director- Neuromuscular Center, Boston Children's Hospital. Dr. Darras' research is focused on the molecular genetics, diagnostics and therapeutics of pediatric neuromuscular diseases.



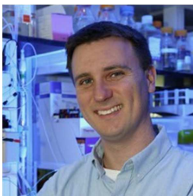
Alexandra Davies, PhD: Postdoc with Georg Borner, Max Planck Institute of Biochemistry, Germany. The focus of Alex's postdoc research involves studying AP-4 function in neurons.



Darius Ebrahimi-Fakhari, MD, PhD: Child Neurology Fellow at Boston Children's Hospital / Harvard Medical School. Dr. Ebrahimi-Fakhari has a long-standing interest in childhood-onset neurometabolic-, neurodegenerative-, and movement disorders. His group is leading two research projects on SPG47: "Development of iPSC-Derived Neurons from Patients with AP-4-associated Hereditary Spastic Paraplegia to Support an Unbiased Phenotypic Screening for Novel Therapeutic Targets" and "An International Registry and Natural History Study For AP-4-associated Hereditary Spastic Paraplegia".



Dr. John Fink: Professor, Department of Neurology, Director, Neurogenetic Disorders Program, University of Michigan. In addition to being one of the world's foremost investigators of upper motor neuron disorders, Dr. Fink also maintains the largest clinic in the U.S. for persons with HSP or PLS.



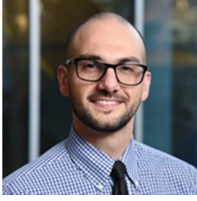
Dr. Steven Gray: Associate Professor at UT Southwestern Medical Center. Dr. Gray's core research focus is to develop adeno-associated virus (AAV) gene transfer vector systems, for clinically-relevant global gene transfer to the central and peripheral nervous system.



Dr. Jennifer Hirst: Principal Research Associate, Robinson lab, Cambridge Institute for Medical Research. Dr. Hirst is a cell biologist who discovered the AP-4 and AP-5 adaptor complexes and has been studying their function and link with Hereditary Spastic Paraplegia.



Robin Kleiman, PhD: Senior Director, Translational Cellular Sciences, Biogen. Dr. Kleiman's team within Research and Early Development is focused on establishing translatable human disease models of CNS disorders to enable testing of novel therapeutic molecules.



Andrés Moreno De Luca, MD: Associate Neuroradiologist & Assistant Professor at Geisinger. Dr. Moreno De Luca's research focuses on the discovery and characterization of genomic variation in individuals with developmental brain disorders, including cerebral palsy, intellectual disability, autism, and epilepsy, as well as correlating genotype with clinical and neuroimaging phenotype by genetic sub-type.



Professor Margaret (Scottie) Robinson: Principal Investigator, Cambridge Institute for Medical Research. Prof Robinson has worked on identifying and characterizing adaptor protein complexes for 30 years.



Mustafa Sahin, MD, PhD: Director, Translational Neuroscience Center, Professor in Neurology, Harvard Medical School. Dr. Sahin's lab investigates the normal cellular functions of signaling pathways implicated in neurological disease. His research is focused on proteins affected in TSC and SMA.



Sarah Sheikh, MD MSc MRCP: Executive Director of Neuroscience Clinical Development, I&I, at Celgene. Before joining Celgene, she held leadership positions of increasing responsibility in clinical development at Biogen where, most recently, she was the Head of Multiple Sclerosis and Neurorepair and the director of the Anne Young (MGH-Biogen) Neurology Fellowship Program.

### Meeting Agenda:

1. Brief introductions (12:00 - 12:15)
2. Presentations:

#### Block 1: The science of AP-4-HSP and progress to date

- a. AP-4 cell biology, Alex Davies (12:15 – 12:35, including 5 minute Q&A)
- b. AP-4-HSP Natural History Study update, Darius Ebrahimi-Fakhari (12:35 – 12:55, including 5 minute Q&A)

10 minute break (12:55 – 1:05)

- c. Gene therapy for SPG47 update, Mimoun Azzouz (1:05 – 1:25, including 5 minute Q&A)
- d. Gene therapy for SPG50 update, Xin Chen (1:25 – 1:45, including 5 minute Q&A)

10 minute break (1:45 – 1:55)

- e. Lessons from the GAN Clinical Trial, Dimah Saade (1:55 – 2:15, including 5 minute Q&A)
- f. AP-4-HSP Drug Screening update, Darius Ebrahimi-Fakhari (2:15 – 2:35, including 5 minute Q&A)



Block 2: Discussion topics

3. Discussion topics/Open Discussion (2:35 - 4:00)
  - a. What crucial knowledge gaps need to be addressed next?
  - b. What are the best short and long term approaches to finding a cure for AP-4-HSP?
    - Next steps for the Natural History Study?
    - Next steps for the preclinical development of gene therapy vectors?
    - Next steps for approval by regulatory agencies and clinical trial design?
4. Conclusion and review of next steps

**\*\*\* Cocktail reception and dinner to follow at the  
Longwood Inn, 342 Longwood Ave. Hosted by Cure AP-4! \*\*\***

**Cure AP-4 Family Meet and Greet: 11/02/2019**

***Hosted by Cure AP-4***

**Meeting location:** Boston Children's Hospital  
Patient Entertainment Center  
Berthiaume Family Building  
300 Longwood Ave Boston, MA 02115

**Meeting Time:** November 2<sup>nd</sup>, 10am to 1pm

**Contact phone:** Kasey Edwards: (781) 405-8961

**Parking:** Corner of Longwood Avenue and Blackfan Circle (Boston Children's Hospital patient garage)

Please come and meet other families affected by AP-4-HSP. This will be a casual event, with child entertainment, to meet and network with other families, talk with any attending researchers, and for the kids to connect in person. Lunch will be provided.

