

Cure AP-4 Research Conference: 10/22/2020

Graciously hosted by BCH Translational Neuroscience Center

Meeting Time: October 22nd, 9:30am to 1pm Eastern Time

Contact phone: Jessica Kim, Administrative Assistant for Translational Neuroscience Center
(617) 919-6258

Zoom Meeting: Join from your computer or mobile device:
<https://bostonchildrens.zoom.us/j/97522144488?pwd=ejYyNDVCZlg1TGpEbHdHNXltWmdEdz09>

Password: 820890

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)

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EWS link: <https://zoom.us/jc/97522144488/join>

Meeting ID: 975 2214 4488

Introduction:

Welcome to the fourth annual AP4-Associated HSP Research Conference! Some exciting new developments in the ongoing gene therapy and drug screening projects will be presented, as well as a progress report on the Natural History Study and International Patient Registry. We look forward to some productive discussion this year about next steps for each of these efforts.

The purpose of this meeting is to:

- Recap what has been learned about AP-4 HSP
- Discuss progress in the ongoing research projects
- Explore options for human phase 1 trials and gene therapy commercialization

On behalf of the families affected by AP-4-HSP, we truly appreciate your willingness to participate in this effort. We are 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: *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:



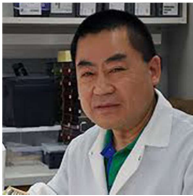
Dr. Mimoun Azzouz: *Chair of Translational Neuroscience, ERC Advanced Investigator, Director of Research and Innovation, University of Sheffield.* Dr. Azzouz has a long-standing interest in developing gene therapy approaches for neurodegenerative diseases. His team utilizes viral-based gene transfer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



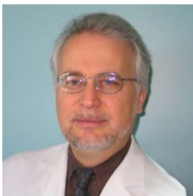
Dr. Craig Blackstone: *Director, Movement Disorders Division, Department of Neurology, Massachusetts General Hospital and Harvard Medical School.* Dr. Blackstone's laboratory investigates the cellular and molecular mechanisms underlying hereditary movement disorders. Craig is one of the most prominent 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, MD, 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 now leading the work as a Co-PI on gene therapies for SPG50 and multiple other neurological disorders under the 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.



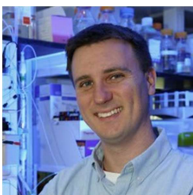
Alexandra Davies, PhD: *Postdoc with Georg Borner, Max Planck Institute of Biochemistry, Germany*. The focus of Alex's postdoc research involves studying AP-4 function in neurons.



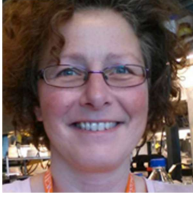
Darius Ebrahimi-Fakhari, MD, PhD: *Child Neurology Fellow at Boston Children's Hospital / Harvard Medical School*. Dr. Ebrahimi-Fakhari has a long-standing interest in childhood-onset neurometabolic-, neurodegenerative-, and movement disorders. His group is leading several research projects on AP-4-HSP including "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.



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 childhood neurological diseases. His research is focused on proteins affected in Tuberous Sclerosis and related neurodevelopmental disorders.



Sarah Sheikh, MD MSc MRCP: *Senior Vice President, Neuroscience at Takeda*. Before joining Takeda, she held leadership positions of increasing responsibility in clinical development at Celgene and Biogen.

Meeting Agenda:

1. Brief introductions (9:30 - 9:45)
2. Presentations:

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

- a. AP-4 cell biology, Alex Davies (9:45 – 10:05, including 5 minute Q&A)
- b. AP-4-HSP Natural History Study update, Darius Ebrahimi-Fakhari (10:05 – 10:25, including 5 minute Q&A)

10 minute break (10:25 – 10:35)

- c. Gene therapy for SPG47 update, Mimoun Azzouz (10:35 – 10:55, including 5 minute Q&A)
- d. Gene therapy for SPG50 update, Xin Chen (10:55 – 11:15, including 5 minute Q&A)

- e. AP-4-HSP Drug Screening update, Darius Ebrahimi-Fakhari (11:15 – 11:45, including 5 minute Q&A)

10 minute break (11:45 – 11:55)

Block 2: Discussion topics

- 3. Discussion topics/Open Discussion (11:55 - 1:00)
 - a. Cure SPG52 gene therapy options
 - b. What crucial knowledge gaps need to be addressed next?
 - c. 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

