Cure SPG47 Advisory Meeting: 12/20/2018

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: 1pm to 5pm

Contact phone: Lea Florentino, 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/696362119

Or dial in from your telephone:

Internally: x28882
646-558-8656 (Primary)
408-638-0968 (If you are unable to dial into the primary number)

Or iPhone one-tap:

+16465588656,,696362119# or +14086380968,,696362119#

EWS link: https://zoom.us/wc/696362119/join

Meeting ID: 696 362 119

Introduction:

During the first ever face-to-face meeting of CureSPG47 families and medical advisors in March 2017, various possibilities for research and treatment were discussed, including tradeoffs and probability of success. A consensus was reached that gene therapy offered the greatest hope for meaningful treatment during the lifespan of SPG47 patients identified at the time, and in consideration of the financial resources of the CureSPG47 non-profit organization. Soon after that initial meeting, CureSPG47

entered into a research agreement with the University of Sheffield, with Dr. Mimoun Azzouz as the Principal Investigator leading an effort to develop a working AAV9 viral vector proof-of-concept with an AP4B1 KO mouse model.

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 neurons is now underway. Also under leadership of Dr. Ebrahimi-Fakhari, the first ever AP-4 natural history study and patient registry are underway. Over 95 AP-4 patients (~35 are SPG47) have agreed to participate in this critical effort to date, which has helped to confirm a new level of worldwide awareness and prior misdiagnosis for patients with similar symptoms.

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

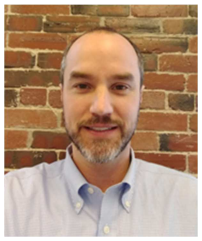
- Recap what has been learned with regard to SPG47
- Discuss progress in the ongoing research projects
- Discuss applicability of successes with other rare diseases
- Explore the most expedient options for obtaining regulatory approval for future human clinical trials

On behalf of the families affected by SPG47, we truly appreciate your willingness to participate in this effort. We are extremely fortunate to have so many impressive people involved in the effort to cure and/or treat this devastating disease!

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: *Product Development and Commercialization Lead, Biogen.* Erika has over 20 years' experience in healthcare and biotech, leading several cross-functional areas focusing on product program management, patient services programs, marketing and health care administration.

Cure SPG47 Network of Medical and Scientific Advisors:

Dr. Irina Anselm: *Assistant Professor of Neurology, Harvard Medical School*. As the Director of the BCH Mitochondrial Program, Dr. Anselm applies the latest techniques to help patients and their families manage their disorders. One of her top concerns is improving the quality of life for patients through the study and development of new drugs and therapies.

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. Gerard Berry: *Director, Metabolism Program, Boston Children's Hospital, Specialist in Genetics and Genomics, Professor of Pediatrics*. Dr. Berry specializes in metabolic and genetic disorders, and is certified in pediatrics, biochemical genetics and pediatric endocrinology.

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.

Wendy K. Chung, MD, PhD: *Associate Professor of Pediatrics (in Medicine) Columbia University Institute for Genomic Medicine*. Dr. Chung is a board certified clinical geneticist with a PhD in molecular genetics. She is the director of the clinical genetics program at Columbia University, a co-director of the molecular genetics diagnostics lab, and heads a research laboratory in the division of molecular genetics investigating the genetic bases for a variety of Mendelian and complex traits.

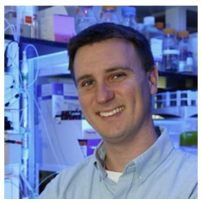
Dr. Basil Darras: *Associate Neurologist-in-Chief, Chief-Division of Clinical Neurology, Director- Neuromuscular Center, Boston Children's Hospital*. Dr. Darras' research is focused on the molecular genetics, diagnostics and therapeutics of pediatric neuromuscular diseases.

Alexandra Davies: *PhD candidate, jointly supervised by Dr. Borner (Max Planck Institute of Biochemistry, Germany) and Professor Robinson, Cambridge Institute for Medical Research*. The focus of Alex's PhD research involves studying the AP-4 adaptor complex using CRISPR CAS9 and other tools.

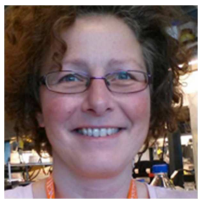
Darius Ebrahimi-Fakhari, MD, PhD: *Child Neurology Fellow at Boston Children's Hospital / Harvard Medical School.* Dr. Ebrahimi-Fakhari has a long-standing interest in childhood-onset neurometabolic-, neurodegenerative-, and movement disorders. His group is leading two research projects on SPG47: "Development 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. Florian S. Eichler: *Director of the Leukodystrophy Service, Mass General Hospital*. Dr. Eichler's research focuses on genetics of peroxisomal disorders, lipid metabolism, and spatial aspects of nuclear magnetic resonance spectroscopy. He currently holds several NIH awards funding studies to analyze metabolic changes seen in the brain by MR measures and to determine the neurotoxicity of newly discovered atypical sphingolipids.

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.

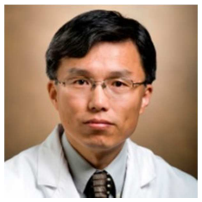


Dr. Steven Gray: *Assistant Professor at UNC School of Medicine Gene Therapy Center*. Dr. Gray's core research focus is to develop adeno-associated virus (AAV) gene transfer vector systems, for clinically-relevant global gene transfer to the central and peripheral nervous system.



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.



Dr. Jun Li: *Professor of Neurology, Vanderbilt University School of Medicine.* Dr. Li's research is focused on myelin biology and the pathogenesis and therapeutic development of inherited peripheral nerve diseases.

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.

Sharon Tooze: *Molecular Cell Biology of Autophagy Laboratory Group Leader, Francis Crick Institute, London, UK.* Sharon's lab has identified several mammalian Atg proteins since 2006 and continues to contribute to understanding of autophagy at the molecular cell biology level.

Meeting Agenda:

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

Block 1: The science of AP-4-HSP

   a. AP-4 cell biology, Alex Davis (1:15 – 1:35, including 5 minute Q&A)
   b. AP-4-HSP clinical and translational, Darius Ebrahimi-Fakhari (1:45 – 2:05, including 5 minute Q&A)

10 minute break (2:05 – 2:15)

   c. Basic science of HSP, Craig Blackstone (2:15 – 2:35, including 5 minute Q&A)
   d. Gene therapy for AP-4-HSP, Mimoun Azzouz (2:35 – 2:55, including 5 minute Q&A)

10 minute break (2:55 – 3:05)

Block 2: Learning from research on other diseases

   e. Preclinical research in rare disease - the industry perspective, Robin Kleiman (3:05 – 3:15)
   f. Research approach to CP, Andrés Moreno De Luca, MD (3:15 – 3:25)
   g. Clinical trials in rare diseases - the example of X-linked ALD, Florian Eichler (3:25 – 3:35)

3. Discussion topics (3:35 -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?
4. Open Discussion (4:00 – 4:50)
5. Conclusion and review of next steps