Clinical trial readiness for Hereditary Spastic Paraplegia: Lessons learned from translational research in rare diseases.

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After introducing himself, and thanking the Spastic Paraplegia Foundation for the opportunity to speak, Dr. Fakhari listed his disclosures on the screen, which included research grants from NIH/NINDS, CureAP4 Foundation, Tom Wahlig Foundation, Manton Center for Orphan Disease Research, BCH Office of Faculty Development, BCH Translational Research Program. Joint research agreement with both Astellas pharmaceuticals Inc. and Blackfin Bio Inc. Royalties from Cambridge University Press. Consulting work with Health Advances LLC, BlackFinBio Inc., University of Texas. Speaker honoraria from Movement Disorders Society, and Taiwan Society of Child Neurology. Scientific Advisory Board (volunteer): Cure AP4 Foundation, the Maddi foundation, SPG 69/Warburg Micro Research Foundation, the Lily and Blair foundation, Genetic Cures for kids Inc.. local advisory committees (volunteer): Gene Therapy Scientific Review committee. International Advisory Committee's (volunteer): Movement Disorder Society – Task Force on Pediatric Movement Disorders.

In this talk, Dr. Fakhari plans to cover three principle topics. First, he will talk about what clinical trial readiness is and what the challenges are for Hereditary Spastic Paraplegia and Primary Lateral Sclerosis, in particular. He will then use the example of some of the other work they are doing at the Boston Children's Hospital looking at a specific groups of childhood onset Hereditary Spastic Paraplegia's, the AP4 types of HSP, to give us an example of how they develop clinical trial readiness. In the last part, he will give an outlook on what we talked about earlier today, the creation of what we are calling the Spastic Paraplegia Center for Excellence Research Network (SP-CERN) that will

cover both clinical research and translational research for both HSP and PLS.

There are many challenges of studying rare diseases. When they talk with regulating agencies and funding agencies, it is important to remember that we are working on a rare disease which offers us unique challenges. As a field, we know that in working with Rare Diseases which by definition affects less than 200,000 people in the US, rare diseases as a group affect over 350 million people worldwide. He thinks Rare Diseases are gaining a voice on the world stage.

Unfortunately, over 95% of the 7,000 rare diseases have no clinical treatment. He thinks there is a reason to be optimistic. We are learning a lot about Rare Diseases driven by genetics, which is a very fast growing field of knowledge. Now the burden is on our SP-CERN to translate these discoveries into therapies. He showed a graph of how studies on Rare Diseases have been growing tremendously over the years and so have FDA and EMA approved drugs and medical products but not nearly at the same pace.

While they are learning a great deal about the genetics of rare diseases, they have, as yet, not been able to readily counteract the affect of certain genes once they understand their function. In many cases with Rare Diseases Clinical Research Networks need to be developed and this is where SPF has done tremendous work over the years developing disease models for HSP and PLS.

On the clinical side, we are missing a lot of data regarding phenotyping and natural history studies. Historically, there has been limited interest on supporting research for rare diseases, but that has changed dramatically. He will highlight some examples.

One of the drivers for this traumatic change has been the fact that genetic testing has become so much more affordable. This means that many more people will have access to it and we will be getting good diagnoses earlier. This will, overtime, improve care. We will also learn that there is a unique disease ecosystem when it comes to developing therapies. So, we know that many diseases are rare (< 200,000 in US), and some might even be called ultra rare (< 12,000 worldwide), micro rare (< 300 worldwide), and even nano rare (<30 worldwide).

As you can imagine, the drug development system we have developed in this country over the last 60 years or so is not built for rare diseases. We have to rethink this, and as we are approaching this era of genomic treatments or therapies, we need to think about how to develop models where we can make these discoveries that need tremendous resources to develop even for the rarest of diseases. That is a unique challenge of the next decade, he thinks. One solution is in developing platform technologies so we don't have to reinvent and go through every step for every disease.

His group at the Boston Children's Hospital is taking on two big challenges. These two challenges are for the rare disease field in general. They are creating clinical trial readiness. What he means, by this entails, generally creating a community around eight different processes: advocacy and fundraising, genomics platform, Registry and natural history data, bio-marker, and HrQoL, preclinical models and tools, toxicology studies, GMP manufacturing, and regulatory landscape.

The second challenge is to develop genetic molecular based treatments. These come in different modalities. He put up a chart that looked something like the following:

Modality	**Cause of disease at the**	**Protein level**	**Molecular Target**
	Reduction of loss of function	Excessive or detrimental function	DNA > RNA > Protein
Small molecule	*******	******	***** ***** *****
Protein replacement	*******		*****
Antibody		*******	*****
Oligonucleotide therapy	*******	*******	*****
Cell and gene therapy	*******		*****

We are entering a different situation that is becoming a reality for some genetic diseases. In the field of pediatric neurology a lot of what we have learned has come from the field of Spinal Muscular Atrophy (SMA) where we now have 3 approved therapies that work on the molecular mechanisms and have changed outcomes dramatically. This is continuing. Just yesterday or the day before the FDA granted accelerated approval for a new gene therapy for Duchenne Muscular Dystrophy.

This is setting the stage for similar approaches from other diseases. This is a very exciting time, and we are learning a lot from these relatively more common rare diseases. As we are building, these fancy therapies, we have to think about how we can be ready for them. As a metaphor for the current state of HSP research, he put a picture of a country, gravel road and compared it to another photo of a fancy sports car on a nice road, saying that there is a road and a mechanism, and we just have to build it. That is what clinical trial readiness really means.

To give this a bit of historic background, he put up a chart that showed how HSP research and knowledge has progressed since

the 19th century. It was first described by Strumpell in 1880 as “familial spastic paraplegia” and by Lorrain in 1888 in German & French literature that basically described the symptoms. It became known as Stumpell Lorrain disease. In the 20th Century we understood the pathology better when it was studied by Schwarz in 1952 with imaging studies that could look at the brain and spinal cord using CT & MRI scans.

In the 1990s genetics came around and they started realizing that HSP is not one condition but is actually caused by a group of different genes. We are finally at the stage, based on all this knowledge, when we are starting to see the first interventional trials. If we can translate some of the new technologies that he listed earlier, and make them feasible for HSP patients, we will see a lot more therapeutic approaches becoming available to patients.

He started working on childhood onset, HSP, several years ago. Two of the main parts of their work has been a registry and a natural history study specifically for children and young adults with Hereditary Spastic Paraplegia. By March of this year, they had seen over 450 children with HSP. They are trying to see these children on a longitudinal basis and have been trying to see them every year. They have now seen a number for their second and third visit. A lot of this work is coordinated by Amy Tan who was in the audience that day. She has done an outstanding job, coordinating all these complex tasks and assessments.

Over the last three years of working on this study, they have learned a lot. First of all, they have learned about the impact of Denovo variants for dominant forms of HSP and the predominant kinds are, of course, SPG4 and SPG3A. They are also working with Autosomal Recessive forms, the most common of which are SPG11, SPG15, AP4 HSP (AP4 subunits) and SPG49. They are understanding the symptoms better.

None of this is done in isolation. While their studies have been at The Boston Children's Hospital, in all of their projects they work with partners worldwide because in rare disease, that is what you have to do. It is the only way to make progress. They are trying to remedy the fact that over 30% of HSP patients do not have a known HSP's gene and they hope to remedy this problem with new genetic science.

He is now going to talk about Clinical Trial Readiness for people with HSP and use, as an example the work he has been doing with AP-4 related HSP. AP4 are four conditions that are all rare and they are SPG47, SPG50, SPG51 and SPG52. What they have in common is that their proteins are part of the same protein complex. So, they work together and it doesn't really matter which subunit is missing, the complex isn't formed properly when one of them is missing.

Children with the different AP4 related genes, all share the same symptoms. They think of this as one disease caused by four different genes. There was little known about this disease when they started working on it but through the support of many, many families, all around the world, they are much better understanding the symptoms. By focusing on the symptoms they are understanding how to be ready for clinical trials through clinical outcome measures.

With this particular type of HSP, they are learning that it progresses from a stage of low muscle tone in the first year of life to spasticity in early childhood and that spasticity worsens through childhood usually involving just the legs but can also involve the arms as well. They have learned that this is both a Neuro developmental and a progressive neurological disease disorder. This means that the disease begins so early that it might be the result of an early developmental process where some of the progressive features are part of the ongoing disease process.

One important aspect that all of the participating families have contributed to is for them to understand what symptoms really matter. They used a health related quality of life questionnaire that had been developed for children with cerebral palsy to measure health related quality of life, and correlate them with symptoms. What they learned from this is really a snapshot of what matters to families. They learned that the degree of spasticity and the degree of mobility, really correlates with health related quality of life where, as other things like the number of seizures did not. This basically quantifies what families tell them. That is important when they talk to regulatory agencies because they then have a way of communicating what is important to the families in the community that they serve. This will be important as they develop new therapies because they need to make the case that these therapies really do improve the quality of life.

He put up a chart that showed how things change over time for people with AP4 associated HSP. Once we begin testing treatments, we will be able to compare them against our previous longitudinal studies to see how much better people using the treatment are living than the historical record of a large cohort of other patients.

They are also very interested in developing bio markers, which will greatly help measure the efficacy of any treatments. They tried to discover if NFL or Neuro Filament Light chain (which is really a structural protein of long axons), which is a very good biomarker for other diseases like multiple sclerosis could work for AP4 related HSP diseases and discovered that it is elevated only modestly. This is different from other forms of HSP, where they have found higher levels.

They also tried to consider markers of glial cells in the brain, and they did not detect a change. They conclude that this particular kind of HSP is predominantly a neuronal problem, and does not really effect the white matter or glial cells of the brain.

With the very recent creation of the SP-CERN, we hope to thoroughly study most forms of HSP and PLS and really take it to the next level. The first one main goal of the SP-CERN is to reach a level of clinical trial readiness. We all know that national and international collaboration is essential for this. It is essential for the development of new diagnostic tools and therapies. They are developing a US network that is carefully designed to have a vital infrastructure to generate proof of concept data to allow them to establish a network that can incorporate clinical trials in the future.

The three aims are: 1. to establish the SP-CERN. The second is to establish an essential research protocol. It is also an effort to coordinate and harmonize with partners in Europe for example as similar efforts exist there. They plan to compare data and pool and join forces. They are developing this infrastructure to test key elements of this consortium to appeal to funding agencies to demonstrate them as valuable long term.

He listed the first proposed centers in the United States, and they include Daniel Calame, MD, PhD at Texas Children's Hospital, Michelle Christie, MD at UT Southwestern Medical Center, Michael Shy, MD at the University of Iowa, Healthcare, John K. Fink MD at the University of Michigan, Medical Center, Darius Ebrahimi-Fakhari, MD, PhD at Boston Children's Hospital, Charles Blackstone, MD, PhD at Massachusetts, General Brigham, Hiroshi Mitsumoto MD at Columbia University, Stephan Zuchner MD, PhD and Mario Saporta, MD, PhD at University of Miami, Miller School of Medicine and Marie Davis, MD, PhD at University of Washington. As our SP-CERN develops, we are hoping that other medical centers will join us for an even better geographical distribution in the United States.

They anticipate three major lines of research. The first will be developing a central clinical research database which he named

the central REDCap database housed at the Boston Children's Hospital. They will measure. Clinician reported, outcome measures, patient reported, outcome measures, health related quality of life measures, neuro-imaging, and video archive (de-identified) every 12 months. They will also collect bio samples at the central bio bank at the Massachusetts General Hospital managed by Dr. Charles Blackstone. Samples will include plasma/serum, DNA, RNA, PBMC or fibroblasts, and other bio specimens. They will be also developing a genomics database and collect the information at the sequencing facility, and central genomic archive at the University of Miami led by Dr. Stephan Zuchner. There, they will be doing whole genome sequencing, long read sequencing, RNA sequencing, and Curation and analysis in their genesis platform. They plan to share all this data on a global level.

So what are the milestones that they hope to achieve in the next two years? The first goal is for them to develop an operational plan. There are several other consortia that have developed this same idea very successfully, which we can learn from. We will follow their lead. We will develop an operational plan that coordinates all the centers across the country.

The second aim is to develop a central research protocol and IRB approval. This is crucial from an administration standpoint to do this early, so this will be our first order of business. What the first two years will actually show us is that if the net work is really operational and can enroll at least 100 patients with PLS and HSP in a shared clinical data base. They will be doing bio- banking of blood samples from those 100 HSP & PLS patients in a shared bio bank. They will also complete whole genome sequencing of 15 patients with suspected HSP and PLS.

This will basically be building and testing the system. From a long-term perspective, the idea is to develop a system that warrants sustainable funding on a national level from NIH. There are institutes that we are interested in joining such as the NIH/

national center for advancing translational science (NCATS) and the Rare Diseases Clinical Research Network (RDCRN). We will be applying for funding from these programs. There are others, including a program from the US FDA that is looking to support natural history studies as well. The point here is that we are using seed money to build the infrastructure and to test the system to make sure we are ready for sustainable national funding. They want to continue to develop this for the years to come and to be ready for clinical trials as soon as possible.

To summarize his entire talk, Dr. Fakhari said, 1. There are unique challenges, but also opportunities for creating therapies for Rare Diseases including HSP and PLS. 2. Broad access to genetic testing and longitudinal natural history studies are key to establishing clinical trial readiness. 3. Collaborative research into HSP and PLS is critical to building comprehensive programs for diagnostic progress and clinical trial readiness to support the development of novel therapeutic approaches.

Dr. Ebrahimi-Fakari then closed by thanking the audience and taking a few questions.