Hereditary Spastic Paraplegia's Biology

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After introducing himself, and expressing his gratitude for the opportunity to speak, Dr. Blackstone said that he would be speaking about the biology of hereditary, spastic paraplegia, which is important in ultimately getting to a cure. It links into both the subjects that Dr. Zuchner has just talked about and that which Dr. Darius Fakhari will be talking about later today.

He also introduced the institution where he works, which is Massachusetts General Hospital, movement disorders, division, department of neurology. He first shared his disclosures, which included his being a chair of the Scientific Advisory Board and board of directors of Asha Therapeutics, his position on the Scientific Advisory Board of NKGen Biotech, his work as consulting for FirstThought, Mendel Group, GuidePoint, Health Advances and his research funding from NINDS, MGH, and philanthropy. His experience of being a consultant actually gives him the experience of working with companies, understanding what they want, and helping them move ideas from academics to practical help for patients.

He hopes, and feels confident that the expertise of each member of our SP - CERN will bring very valuable levels of expertise that will work synergistically to move toward cures as quickly as possible.

He showed a picture of Massachusetts General Hospital, which is the oldest hospital in Boston. It is well over 200 years old and is also the largest hospital based research program in the United States. It has the largest neurology department in the United

States. There are over 300 neurology faculty at Massachusetts General Hospital and many of them do research.

His job at MGH is as Chief of the Movement Disorders Division, so he oversees over 40 faculty and in that division they have over 5 Centers of Excellence. They have Turrets Syndrome, Huntington's Disease, Parkinson's Disease, Linked Dystonia Parkinsonism and Progressive Supranuclear Palsy.

They are now more than happy to add our new SP-CERN to their family of Centers of Excellence. They have learned a lot about running these networks from this experience of working with other Centers of Excellence. All of those centers of excellence are supported by foundations. Overtime, they will have the ability to transfer the knowledge they have gained from working with other centers of excellence, and their supporting foundations to make sure that this net work succeeds, and to move us forward toward significant help for people with HSP and PLS. All of the other centers of excellence that they are working with are involved in clinical trials right now and this is what they hope for our new SP - CERN.

Boston is an old city which is large and so very hard to build in so their laboratories are not in Boston, they are across the river in Charlestown. His lab is just around the corner from a very famous boat called the USS Constitution. The Navy used to have a very large dock in the Charleston Harbor which has usually been used only during wartime. Most of this area is used by the Navy to allow people to visit the oldest ship in the U.S. Navy. A lot of the Old Navy buildings have been re-purposed as research labs. They have one building that is completely dedicated to neuroscience and Neurodegenerative disease research.

He started his discussion of HSP and PLS biology by talking about circuitry. HSP and PLS share problems with upper motor neurons. He displayed a diagram of the upper motor neuron,

which starts in the upper brain and descends all the way through the spinal column. People usually think of cells as being very small, but these cells can be a meter long or about 40 inches which are very big and these are the cells that are predominantly affected with HSP and PLS. It is length dependent, and that is why HSP people have affected legs because legs are at the far end of those cells.

People with PLS do not necessarily have that length dependency. They have upper motor neurons involved in other ways. That is why people with PLS have problems in other areas of their body, such as arms, swallowing, and speech. The commonality is the type of cell that is involved. That is part of a motor pathway, so the corticospinal nerves synapse onto other nerves that allow for movement.

Most people with upper motor neuron problems do not have a lot of weakness, but they do have spasticity. This is the link between these two diseases and this is the reason why the Spastic Paraplegia Foundation is working on both diseases.

HSP is also described by the different genes that effect the mechanism of this long cell. The genetic efforts of our SP - CERN is very important because we need to have the ability to genetically diagnose more people with HSP (currently about 30% are not genetically diagnosed). The specific genetic diagnosis is important, because that will determine the treatment that a person will receive.

HSP is rare (2-9/100,000 people). PLS is much rarer and because of this it can sometimes "fall through the cracks". They see many PLS patients in ALS clinics, and when they discover they do not have ALS, where do they go? This new SP — CERN is very important because it will allow people with PLS to have a clinical home to go to. It will be a clinical home for clinical trials in the future.

One big advantage we have with HSP's in particular (and as they study the genetics of PLS they will get some insights there too) is that HSP has many known causative genes. They can study the mechanisms of those particular known HSP genes and have an opportunity to overcome what is malfunctioning. Many other diseases such as Alzheimer's and Parkinson's do not have known genes, so they do not have that advantage.

He then put up a list of different HSP and PLS treatments which included: 1.Physical and occupational therapy, stretching, activity. 2.Decreased spasticity (Anti-spasmodic's – baclofen, tizanidine; baclofen pump). Dantrolene use often limited by weakness. 3. Pain, relief, facilitate self-care (targeted Botulinum toxin injections) 4. Dystonia (levodopa, trihexyphenidyl) 5. Spastic bladder (oxybutynin, tolterodine) 6 Spasms (benzodiazepines). 6. Other agents such as dalfampridine occasionally helpful. 7. Different stimulation paradigms, wearables. These are all treatments for the symptoms of HSP and PLS but they do not deal at all with the causes of the diseases.

Their goal is to slow or stop the progression of the disease or better yet to prevent it and/or eliminate it entirely. He displayed a quote from Rudolph Virchow in 1858 where he said: "All diseases are disturbances at the cellular level." Genes make proteins which are the building blocks of cells.

A large proportion of the research that Spastic Paraplegia Foundation has sponsored over the years has had to do with understanding the mechanisms behind the different types of HSP's and how they may be treated or managed. This research has been instrumental in allowing us to get to the place of beginning our SP - CERN. They have learned to consider HSP not as the over 90 different diseases that make it up, but that the mechanisms of the different genes fall into groups of how they affect the cell.

HSP60 affects the Mitochondria. SLC33A1, CYP7B1, B4GALNT1, DDHD1, DDHD2, GBA2, CYP2U1 and CPT1C affect Lipid metabolism. Atlastin-1, spastin, erlin1, erlin2, REEP1, REEP2, seisin, ARL6IP1, RAB3GAP2, reticulon 2, CTP1C and protruding all affect Tubular Endoplasmic Reticulum. NIPA1, spastizin, spatacsin, spartan, spastin, strumplellin, maspardin, AP4, AP5, USP8, VDR48, VPS37A, and TECPR2 all affect Lysosomes/endosomes autophagosomes. PLP, CX47 and FA2H all affect Myelin/oligodendrocytes. All of these are different functional parts of the upper motor neuron.

With every kind of HSP, before we can develop therapies, we need to understand what is broken. Once we see that, we can decide on how to intervene.He showed how many HSP genes link together for their cellular functions. He explained how most animals or insects never get HSP so it is difficult to get a little mouse to mimic a HSP defect unless they try to mutate more than one of those similar mouse genes for full effect.

He showed a film of two mice, the lower one of which was showing HSP walking abnormality because it had more than 1 HSP gene mutated so it can be adequately used for research to show signs of improvement with treatment.

He showed the many, many different ways that the mice are measured so that they can adequately understand what functions are actually not working and what functions are improving with treatments and by how much. The different categories of many different measurements each included Speed, Rotarod and Ledge Test. The extensively detailed measurements are made so that they can have a high degree of certainty regarding how much improvement a treatment will have. They do not want to just look at a mouse and assume there are good improvements taking place. They are currently working with a lab called Jack-

son Labs in Maine, where they are having the lab do it in such a rigorous way that even the FDA will accept.

He talked about how AI technology is currently a high topic of conversation, but they have been using AI for many years. He showed an example of how they used AI over 5 years ago with ER research. They used an AI technology called VIPSAM that simulated the workings of the endoplasmic reticulum in mice. It took a year but they were able to reconstruct the cortical spinal column of a mouse with this AI technology at the highest resolution ever done.

Because they generated so much data with this computer technique, it would have taken people many years to have done it by hand. It took a super computer about an hour to analyze this massive amount of data. He showed a large photograph that the computer displayed and explained that at the beginning the computer made a mistake. The reason why the computer made a mistake is that the mouse with HSP were having problems with its corticospinal neuron that are so abnormal that the computer did not know to look for it. When the scientists looked more carefully, they reprogrammed the computer to look for the horizontal versus vertical arrangement of the ER in the corticospinal neuron and thereby were able to let the computer actually see what was there.

This is what we have always wanted. We want to see the abnormalities in the cell so we can determine what treatments are necessary to remedy them. This is the kind of research that Spastic Paraplegia Foundation has been funding and building on over the years. Dr. Blackstone introduced the idea of children with HSP and how they have been misdiagnosed over the years with Cerebal Palsy. As our SP - CERN is developed and strengthened, it will greatly help to correctly diagnose children with HSP.

He closed by saying that we have learned so much over the years about HSP and PLS so we are now poised to do or make some great progress with our SP - CERN.