SPF SPASTIC PARAPLEGIA FOUNDATION, INC.

Research / Education / Support

2018 ANNUAL REPORT

STEPPING FORWARD TODAY TOWARD A CURE TOMORROW

President's Letter

Dear Friend,

The progress that is taking place with HSP and PLS research is truly amazing and we owe it all to you! Our most sincere and heartfelt thanks go out to you, the community at large and to all of our generous supporters for making this possible. Let me tell you about just some of the highlights of the progress that is taking place with the research we are sponsoring with your generous support.

The Impact You are Making

John K. Fink, MD

John K. Fink, MD, Professor of Neurology, University of Michigan Medical Center, Ann Arbor, MI, is being sponsored by The Spastic Paraplegia Foundation in his study entitled: "Primary Lateral Sclerosis Biomarker Discovery". Dr. Fink also serves as the medical advisor for our Foundation. The objective of his study is to identify biomarkers for **Primary Lateral Sclerosis.** It is essential to develop biomarkers (effective measurements of disease progression) in order to be able to measure whether any future Clinical Trials are effective.

Dr. Fink and his associates are focusing on the analysis of micro (small) RNA in circulating blood. Similar analysis of microRNA has shown promise as a biomarker for ALS.

They will begin by focusing on the methods of analysis. There are many factors that cause variability in both the quantity and specific content of microRNAs in circulating blood. Some of these variables include sample handling (e.g. whether the sample is placed immediately on dry ice and processed within hours); day-to-day fluctuation; and timing (e.g. relationship to meals).

Their current strategy is to simultaneously obtain samples from each subject prior to eating breakfast; and to analyze each sample after a 24 hour delay (If samples are not damaged by the 24 hour delay, it will permit samples to be obtained at sites outside the University of Michigan and greatly facilitate the rest of their study).

Emanuele Panza, PhD

Emanuele Panza, PhD, Assistant Professor in Medical Genetics, Department of Medical Surgical Sciences, University of Bologna, Italy, is being sponsored by The Spastic Paraplegia Foundation in his study entitled: "Understanding **Hereditary Spastic Paraplegia:** Lessons and therapeutic options from a rare form of Hereditary Spastic Paraplegia".

Dr. Panza and his associates mapped the SPG9 form of HSP and recently they identified mutations in the ALDH18A1 gene being responsible for this SPG form.

They are developing in vitro and in vivo models to dissect the pathogenetic mechanism of the disease and to test new therapeutic approaches.

SPG9 is due to the non-synonymous single nucleotide changes c.727G>C or c.755G>A in exon 7 of the ALDH18A1 gene that affect proximate amino acids of the G5K domain (p.Val243Leu and p.Arg252Gln, respectively). These mutations do not prevent production nor cause cellular mislocalization of P5CS. They are loss-of function mutations as evidenced by plasma amino acid analysis and by enzyme activity studies in recombinantly produced human P5CS. They selectively

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inactivate the domain where they map (G5K). P5CS is a high oligomer (possibly an hexameric trimer of dimers). SPG9 mutations disturb the architecture of the P5CS oligomer, making it prone to dissociate to dimers. In silico structural analysis suggests that P5CS mutations can be dominant or recessive depending on whether they affect or not residues involved in intersubunit or interdomain interactions, disturbing or not disturbing the architecture of the oligomer, thus supporting a dominant negative disease-causing mechanism. Recessive and dominant mutations have been identified in HSP (SPG9A MIM601162, SPG9B MIM616586) and in forms of cutis laxa (ADCL3 MIM616603, ARCL3A MIM219150) The generation of a mouse model will be essential to dissect the pathogenetic mechanisms of SPG9 and to test new therapies.

Peter W. Baas, PhD

Dr. Peter W. Baas, PhD, Professor, Neurobiology and Anatomy College of Medicine, Drexel University, Philadelphia, PA is being supported by The Spastic Paraplegia Foundation in his study entitled: "Cause of nerve degeneration in people with **Hereditary Spastic Paraplegia**".

Hereditary Spastic Paraplegia (HSP) can result from the mutation of several different genes, but the most commonly mutated gene is called SPAST or SPG4. SPAST encodes for a protein called spastin, which plays an important role in nerves to regulate the tracks (called microtubules) along which substances move up and down the nerve. When mutated, spastin does not function properly and the microtubules may not be able to carry out their functions as well as they normally do. Some researchers think this is what causes nerves to degenerate in patients with HSP. Dr. Baas and associates have been working on a different idea, which is that the mutant, spastin, imposes toxicity on the nerve that causes it to degenerate.

Contrasting these two ideas can be thought about as a simple analogy to a classroom where the first idea is that a student did not show up for class, but the other idea is that the student did show up for class but is making trouble by misbehaving. Neither is good, but the troublemaking is what causes major problems.

These two ideas for HSP are both defensible, but developing therapies for patients depends on determining which one is true. To do this, they are working with mouse models. One mouse has a SPAST gene deleted, so as to test the idea that the nerve degeneration results from not enough spastin. The other mouse has a mutant form of human spastin introduced into the genome so as to test the idea that the mutant spastin is a trouble-maker. They have found that the mouse with one SPAST gene deleted has mild behavioral deficits, but that the mouse expressing the mutant spastin has deficits very much like patients with HSP. They are performing more studies on these mice, to understand what the toxic effects of the mutant are, whether insufficient spastin might exacerbate the problems caused by the mutant, and also to test potential therapies.

Gerardo Andres Morfini, PhD

Gerardo Andres Morfini, PhD, Associate Professor, University of Illinois at Chicago, is being supported by the Spastic Paraplegia Foundation in his study entitled: "Understanding how mutant Spastin in SPG4 **Hereditary Spastic Paraplegia** affects the intracellular movement of organelles".

Most neurons have a cell body, multiple dendrites, and a long cytoplasmic projection, termed axon, that extends to target cells in a manner analogous to an electrical wire. Unlike man-made wires, axons feature hundreds or thousands of specialized subdomains needed for neuronal communication, including Nodes of Ranvier and presynaptic terminals.

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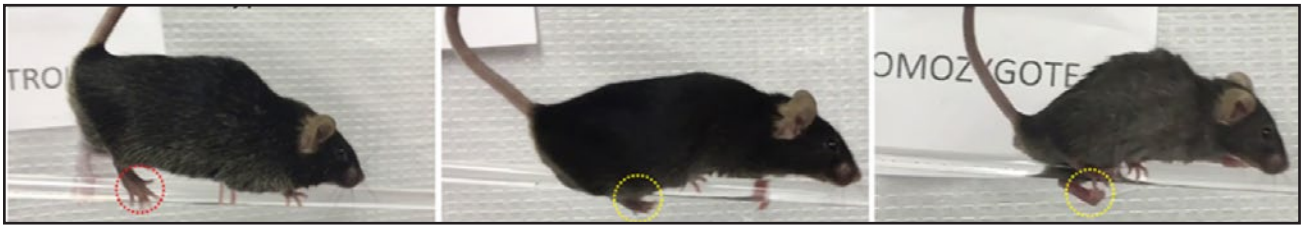

The first panel shows a normal mouse. Middle panel is a mouse with one mutant SPAST gene, and the third panel is a mouse with two mutant SPAST genes. The mice are walking on a beam. Normal mouse does fine, but the mice with the mutant SPAST genes do not walk very well on the beam.

Upper motor neurons, the main cell type affected in Hereditary Spastic Paraplegia (HSP), bear some of the longest axons in the human body. Extending over a yard in length in some cases, these axons connect neuronal cell bodies in the cerebral cortex of the brain to their target cells in the distant spinal cord. It is well accepted that the clinical symptoms of HSP results from degeneration of these axons, but what makes this happen is unknown.

Because the protein synthesis machinery is absent in axons, cellular organelles and protein components needed at these subdomains need to be transported over long distance from their site of synthesis and packaging at the neuronal cell body. This cellular process, referred to as axonal transport, is executed by molecular motor proteins. By allowing the continuous transport and selective delivery of cellular materials at specific axonal subdomains, axonal transport ultimately underlies the ability of neurons to receive, process and transmit information. Interestingly, some forms of HSP results from mutations in genes encoding molecular motor proteins, suggesting that upper motor neurons are uniquely vulnerable to deficits in axonal transport. Despite this knowledge, whether deficits in axonal transport represent a pathological feature common to all HSP variants remained unknown.

Mutations in the SPAST gene account for about 40% of HSP cases. SPAST encodes spastin, a protein involved in severing of microtubules, cytoskeletal elements providing structural support to axons. For a long time, it was thought that HSP forms associated with SPAST mutations (SPG4-HSP) resulted from deficits in microtubule severing, but how such deficits would promote axonal pathology was not obvious. More recently, results from our work challenged this notion, showing that HSP-related mutations confer upon spastin a toxic effect on axonal transport.

Specifically, our work revealed that mutant forms of spastin inhibit axonal transport through a mechanism involving aberrant activation of an enzyme termed casein kinase 2 (CK2), which in turn compromises the function of molecular motors responsible for the execution of axonal transport. Given the well-established dependence of axons on axonal transport, these findings provided a novel mechanism underlying degeneration of axons in HSP. Further, the illumination of this mechanism suggested that CK2 may represent a novel therapeutic target to preserve axonal connectivity in HSP.

With support from SPF funding, and using a novel SPG4-HSP mouse model generated by Dr. Peter Baas, Dr. Morfini and his team are currently evaluating mechanisms by which mutant spastin promotes aberrant CK2 activation, and mapping specific axonal proteins modified by CK2. These studies are expected to reveal additional points of therapeutic intervention and to identify biomarkers associated with axonal degeneration in SPG4-HSP.

Giovanni Stevanin, PhD

Dr. Giovanni Stevanin, PhD, Research Director (INSERM) and professor Ecole Pratique des Hautes Etudes, Institut du Cerveau et de la Moelle epicure - ICM (INSERM/UPMC UMR_S1127, CNRS 7225, EPHE), Pitie-Salpetriere Hospital, Paris, France is being supported by The Spastic Paraplegia Foundation in his study entitled: "Identification of the neuronal transcriptomic signature associated with lysosomal defects in **Hereditary Spastic Paraplegia 11**".

Dr. Stevanin and his team including, Typhaine Esteves, Liriope Toupenet, Julien Branchu, Khalid El-Hachimi and Frederic Darios focus their studies on spinocerebellar degenerations, which include cerebellar ataxias and spastic paraplegias. They have identified 11 causative genes in the last few years which include SPG11, SPG15, SPG26, SPG28, SPG49, SPG46, SPG30, SPG72, SCA22, SAX2 and TORAIP1. They have participated in the identification of others (SCA38, SCA21...) and found unusual inheritance modes in known genes (ADLH18A1/SPG9, GRID2…).

Mutations in the SPG11 gene are responsible for the most frequent form of autosomal recessive spastic paraplegia and account for a large range of motor neuron diseases. Dr. Stevanin and his team reproduced this disease in the mouse and identified a pathological hallmark of the disease that is the accumulation of lipids (lipid aggregates) in a subcellular compartment of the neurons, lysosomes. To understand the molecular changes in the brain of those mice and identify the changes that occur and that could potentially be therapeutic targets, they are analyzing the expression of all genes of the genome.

In a first approach, they are comparing gene expression in various brain tissues between healthy and affected mice according to age. They observed some deregulations that are fitting the pathological process abnormalities. These include a dozen of deregulated genes involved in the lysosomal pathway, in agreement with the role of protein encoded by the SPG11 gene.

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The most deregulated genes were involved in lipid metabolism and in the Wnt signaling pathway, supporting recent studies in SPG11 in which lipid accumulations and developmental abnormalities are implicated. Finally, in agreement with an inflammation process evidenced in late stages and of astrogliosis detected from 8 months of age, numerous genes involved in inflammation and immune reaction appeared deregulated, particularly at the age of 8 months. Astrogliosis is an abnormal increase in the number of astrocytes due to the destruction of nearby neurons from neurodegenerative disease. Astrocytes are critical to scar formation and function to reduce the spread and persistence of inflammatory cells, to decrease tissue damage and lesion size and to decrease neuronal loss.

For the second approach, they microdissected neurons from these mice according to the presence or absence of lipid aggregates and analyzed the gene expression in pools of these cells. Deregulation in cells containing lipid aggregates concerned mainly cytoskeleton, Golgi apparatus, fatty acid biosynthesis and development.

Further analyses are ongoing to identify new interesting targets and decipher the mechanisms involved in this pathology.

Anjou Audhya, PhD

Anjou Audhya, PhD, Associate Professor Biomolecular Chemistry, University of Wisconsin-Madison is being supported by The Spastic Paraplegia Foundation in his study entitled "Identifying underlying causes of **Hereditary Spastic Paraplegia** and creating avenues toward the development of new therapeutic interventions."

The pyramidal motor system in humans directs voluntary movement. In particular, long cortical neurons that extend from layer V of the cerebral cortex into the spinal cord enable skilled limb mobility. The maintenance of these corticospinal neurons depends heavily on axonal transport of proteins, lipids, organelles and other vesicular carriers. Numerous regulators of membrane trafficking and organelle dynamics have been implicated in HSP. and other neurodegenerative diseases. Specific mechanisms underlying most of these disorders remain unknown.

Dr. Audhya studied the tropomyosin receptor kinase (Trk) fused gene (TFG) in SPG57 HSP. Previous studies have tried to show the effect of TFG by showing what happens when it is eliminated. These previous studies have shown that TFG plays an important role in maintaining the integrity and organization of the early Endoplasmic Reticulum (ER) pathway. There is also a reduction in the size of mitochondria in neurites. TFG inhibition slows protein secretion from the ER and alters ER morphology, disrupting organization of peripheral ER tubules and causing collapse of the ER network onto the underlying microtubule cytoskeleton. The artificial nature of over expressing TFG or depleting it using small interfering RNAs (siRNAs) poorly simulates the disease condition.

To more accurately represent natural SPG57 HSP, Dr. Audhya used a combination of structural biology, CRISPR stem cell technology and high resolution imaging to define the impact of the TFG (p.R106C) mutation. They biochemically and genetically defined the impact a mutation within the TFG coiled-coil domain which underlies early onset forms of HSP. They found that the TFG (p.R106C) mutation alters compaction of TFG ring complexes which play a critical role in the export of cargos from the ER.

Using CRISPR mediated genome editing, they engineered human stem cells that express the mutant form of TFG and identified specific defects in secretion from the ER. Their data suggests that the TFG (p.R106C) mutation impairs the function of the coiled-coil domain to generate compact octameric ring-like complexes although it does not fully disrupt or unfold the coiled-coil domain. They also found that although the mutant protein is deficient for normal assembly, the equilibrium can be shifted by lowering the pH. They observed prolonged accumulation of the cargo at punctuate structures throughout the peripheral ER in mutant cells relative to controls, suggesting a delay during transport through the early secretory pathway.

They also noted that control axons rapidly form bundles after emerging from neurospheres. In contrast, neurons expressing TFG (p.R106C) failed to exhibit normal axon fasciculation. Together, these data suggest that TFG plays a distinct role from other regulators of ER function in axon maintenance. They found that iPSC-derived cortical neurons homozygous for TFG (p.R106C) exhibit reduced levels of an important adhesion molecule at the surface of axons, which impedes their ability to self-associate. This defect may contribute to reduced nerve conduction speed, which has been documented in several HSP patients harboring mutations in the TFG N terminus.

There could be two possible reasons why the TFG (p.R106C) mutation causes this defect in the ER. One is that the conformational change in TFG ring complexes impairs their ability to concentrate at the ER/ERGIC interface to promote outer COPII coat dissociation, which is a prerequisite for ER-derived transport carriers to tether and fuse with ERGIC membranes. Alternatively, the loosely assembled TFG (p.R106C) oligomers may not function optimally to organize COPII budding sites, which could preferentially affect the transport of bulky high-

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molecular-weight cargos. The retention of such cargos could subsequently lead to additional consequences, including an elevation of ER stress. ER stress could very well lead to neurodegeneration. Therapeutic strategies to reduce ER stress have been used on several models of neurodegenerative disease with varying levels of success. Their data suggests that some HSPs may also respond to this approach.

Their findings demonstrate that the mutation impairs TFG complex assembly which interferes with its function and disrupts the ability of axons to transfer signals. Long axons of the corticospinal tract are particularly susceptible to relatively modest deficits in protein secretion.


Mimoun Azzouz, PhD

Dr. Mimoun Azzouz, PhD, ERC Advanced Investigator, Chair of Translational Neuroscience, Deputy Head, Neurology Unit Director of Research & Innovation, Sheffield Institute for Translational Neuroscience, Sheffield University, United Kingdom us being supported by The Spastic Paraplegia Foundation in his study entitled: "**SPG15 Hereditary Spastic Paraplegia** Gene Therapy Research".

SPG15 is caused by mutations in the ZFYTVE26 gene, encoding the protein spastizin. These mutations predominantly prevent the expression of full length functional protein. There is evidence that SPG15 has a role in intracellular trafficking as well as protein sorting. Further evidence suggests that SPG15 is involved in the process of disposal of waste within each cell. It has also been implicated in spinal neuron development and growth.

Dr. Azzouz's aim was to harness the gene therapy process to develop a gene replacement therapy for SPG15 to cells of the central nervous system - thereby restoring protein levels and normal function of the protein. The therapeutic lentivirus vector has been successfully cloned, the virus produced and then validated in vitro in HEKI293T cells and fibroblasts. LF-SPG15 has been shown to increase levels of SPG15 MRNA and protein in transducer cells. Studies investigating the ability of the virus to correct the malfunction of SPG15 at the cellular level are ongoing.


Sabrina Paganoni, MD, PhD

Sabrina Paganoni, MD, PhD, Assistant professor, Physical Medicine and Rehabilitation and her team of researchers at Harvard Medical School, Boston, MA are being supported by The Spastic Paraplegia Foundation in their study entitled: "Imaging of Neuroinflammation **in PLS and HSP**". Dr. Paganoni has previously demonstrated that integrated PET-MR and 1H-MRS imaging demonstrates associations between markers for neuronal integrity and neuroinflammation with ALS patients and may provide valuable insights into ALS disease mechanisms.

Both PLS and HSP are characterized by difficulties with the way the Upper Motor Neurons function. But what causes this problem? And why is it important to find out? Clearly, for any disease, the more we know about the underlying biological and molecular mechanisms, the closer we are to finding a cure. In addition, better knowledge could help make the diagnosis faster (reducing uncertainties and misdiagnoses).

Sabrina Paganoni, MD, PhD and her team are trying to find out if neuroinflammation (a type of inflammation that happens in the brain) is implicated in PLS and HSP. Why would neuroinflammation have an impact on the function of the Upper Motor Neurons? Think of the telephone game when you whisper a message and it gets distorted by the time it reaches the last person, and the more outside noise there is, the more the message gets distorted. The brain is trying to send messages to the spine and the Upper Motor Neurons are like telephone cables. If neuroinflammation causes a lot of outside "noise", that could reduce the ability of the Upper Motor Neurons to function properly.

Dr. Paganoni's team has already made a lot of progress and results so far suggest that neuroinflammation plays a role in PLS. People with PLS have much more neuroinflammation than people who don't have PLS and this neuroinflammation is localized to the motor regions, exactly where the Upper Motor Neurons reside. Importantly, the pattern of neuroinflammation is different in PLS compared to ALS (a different disease that can be initially confused with PLS). The brain illustration below shows that the areas of maximum neuroinflammation are different in PLS compared to ALS, suggesting a possible new way of differentiating between the two.

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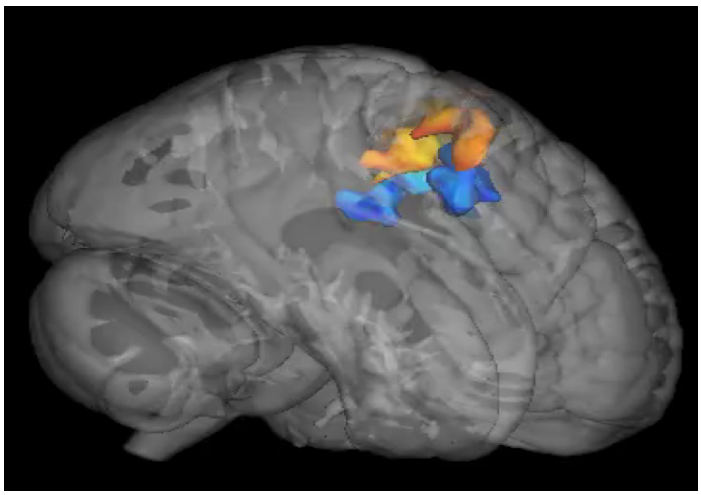
Based on these promising results, the study team has recently started evaluating people with HSP to see if there are similar mechanisms at play, and if so, in which genetic sub-types of HSP.

Results will provide important insights into the causes of PLS, ALS and HSP and will help identify ways to differentiate between these diseases. These results could, in turn, help to develop new therapeutic strategies.



ALS is orange / PLS is blue

Xue-Jun Li, PhD

Xue-Jun Li, PhD, Associate Professor, Department of Biomedical Sciences, Regenerative Medicine & Disability Research Lab, University of Illinois College of Medicine at Rockford; Department of Bioengineering, University of Illinois, Chicago, Illinois is being supported by The Spastic Paraplegia Foundation in her study entitled: "Using Patient Specific Neurons to Explore the Treatment of **HSP and PLS** through Regulating Mitochondria.".

Degradation of human nerve cells is the cause of both HSP and PLS. Mitochondria is the powerhouse of human nerve cells. Dr. Li and her associates will be focusing on uncovering the role of mitochondria in the degeneration of human nerve cells.

In particular, she will identify potential therapeutic strategies by examining whether the nerve degeneration can be rescued by restoring normal function of mitochondria. Earlier she has determined that SPG7 HSP patients do have mitochondrial dysfunction that could be linked to neuronal death.

One unique aspect of their study is that they will use human nerve cells derived from HSP patient-specific s stem cells that are generated from their own skin cells. An important advantage of using these nerve cells lies in the fact that animal and human cells may respond to drugs differently and therefore, these patient-specific nerve cells are very valuable to test therapeutic drugs such as CyclosporinA. Upon successful completion of this study, their next step is to screen drug libraries and test mitochondria-targeting compounds, with the long-term goal of identifying therapeutic agents for HSP and PLS.

Ammar Al Chalabi, PhD,

Ammar Al Chalabi, PhD, Professor of Neurology and Complex Disease Genetics, Maurice Wohl Clinical Neuroscience Institute, King's College London, UK, Director, Instructor in Complex Disease Genetics, Cold Spring Harbor Laboratory, NY & Alfredo Iacoangele PhD, Postdoctoral researcher in Bioinformatics, Department of Biostatistics and Health Informatics, King's College London, UK, are being supported by The Spastic Paraplegia Foundation in their study entitled: "Investigating the Genetic and Environmental Causes of **Primary Lateral Sclerosis**".

Al-Chalabi's collaboration with Robert H Brown Jr, Chair and Professor of Neurology at MGH resulted in the discovery of a chromosome 9p linkage in ALS and frontotemporal dementia. A second related study, with researcher Chris Shaw, now head of the Department of Basic and Clinical Neuroscience at King's College London, further paved the way for the detection of the most common cause of ALS, the C9orf72 mutation. In 2016, Al-Chalabi and colleagues identified new risk variants and found evidence of ALS being a complex genetic trait with a polygenetic architecture, describing four new ALS genes.

Dr. Al Chalabi has won numerous awards, including the Charcot Young Investigator Award from the Motor Neurone Disease Association. He was also honored with the Sheila Essey Prize from the American Academy of Neurology and the ALS Association which recognizes an individual who has made significant research contributions in the search for the cause, prevention of, and cure for amyotrophic lateral sclerosis (ALS) or Lou Gehrig's Disease. ALS is a motor neuron disease

characterized by the gradual degeneration and death of motor neurons in the brain and spinal cord, leading to muscle weakness. People with ALS eventually become paralyzed and die from respiratory failure an average of three years after symptoms first appear.

Professor Al-Chalabi has transformed the way the world thinks of ALS. ALS is now known to be a complex condition in which genetics combine with non-genetic factors, causing degeneration of motor neurons. "When I started, people told me that it was a waste of time looking for genes in those with no family history; now everyone accepts there are genetic causes in everyone with the disease." The study of the genetics of PLS may help answer whether PLS is a form of ALS with perhaps a genetic factor that prevents it from developing into ALS.

The aim of Dr. Al-Chalabi's colleague in this project, Alfredo Iacoangele PhD is the development of a high throughput gene, environment and epigenetics database and analysis system for international ALS research.

Now, Professor Al-Chalabi PhD, Alfredo Iacoangele, PhD and their colleagues are completing two of the largest ALS and PLS genetic studies ever. In one study, researchers are examining 17 million gene variations in 40,000 people. In the other, researchers are sequencing entire genomes of more than 20,000 people. Understanding the genetic causes of ALS and PLS will help researchers understand the reasons motor neurons degenerate, identify the environmental and lifestyle risk factors and allow doctors to design personalized treatments.

Darius Ebrahimi-Fakhari, MD, PhD

Darius Ebrahimi-Fakhari, MD, PhD, Fellow, Child Neurology, Boston Children's Hospital, Harvard Neurology Program, Boston, MS, & Mustafa Sahin, MD, PhD, Co-Investigator, Director - Translational Neuroscience Center, Professor of Neurology, Harvard Medical School, The F.M. Kirby Neurobiology Center, Department of Neurology, Boston Children's Hospital, Boston, MA, are being supported by The Spastic Paraplegia Foundation in their study entitled "Generation of Human Nerve Cells from Children with AP-4 Associated **Hereditary Spastic Paraplegia** to support a Search for New Therapies".

The promise of using human neuron disease models for drug screening is starting to bear fruit across a variety of neurological disorders. Human stem cell derived models

Mustafa Sahin, MD, PhD

of neurological disorders have identified disease relevant traits for disorders including Alzheimer's disease, ALS, Parkinson's disease, Rett syndrome and Tuberous Sclerosis Complex. Induced Pluripotent Stem Cell-based models of at least three forms of HSP, SPG3A, SPG4 and SPG11, have provided new leads into affected pathways and future therapies.

AP-4-associated hereditary spastic paraplegia (HSP), also known as AP-4 deficiency syndrome, is a group of neurodegenerative disorders characterized by a progressive, complex spastic paraplegia with onset typically in infancy or early childhood. Early-onset hypotonia (low muscle tone) evolves into progressive lower-extremity spasticity. The majority of children usually become wheelchair bound. Over time, spasticity progresses to involve the upper extremities. Associated complications include difficulty in swallowing, contractures, foot deformities, dysregulation of bladder and bowel function, and uncontrollable episodes of crying and/or laughing. AP-4-Associated Hereditary Spastic Paraplegia includes the following HSP genes: SPG47, SPG51, SPG50 and SPG52.

Dr. Ebrahimi-Fakhari & Associates will be developing the first human in vitro neuron model of SPG47 HSP by differentiating induced pluripotent stem cells from three individuals with SPG47 and controls as well as two CRISPR-engineered AP4 knockouts and isogenic control lines into excitatory cortical neurons. They will evaluate the form, structure and cellular characteristics of these excitatory cortical neurons, including neuronal form & structure, axon development, trafficking of AP-4 cargo proteins and the orderly degradation and recycling of cellular components.

They will then use these fully developed and studied cell lines to generate a screen that will identify novel therapeutic approaches to treat this disorder via repurposing of FDA approved molecules or other bioactive molecules with well characterized mechanisms of action. Any resulting therapy may be directly applicable to the other AP-4-associated HSPs: SPG50, SPG51 and SPG52.

A screen of this nature may also uncover potential therapeutic mechanisms to treat many other forms of HSP associated with defective membrane or protein trafficking, including SPG4, SPG8, SPG11, SPG15, SPG20, SPG21 and twenty others.

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Holger Sondermann, PhD

Holger Sondermann, PhD, Associate Professor, Department of Molecular Medicine, Cornell University, Ithaca, NY, is being supported by The Spastic Paraplegia Foundation in his study entitled: "Discovery of Novel Mechanisms Underlying **HSP** SPG3A"

Dr. Sondermann is a Fellow of the American Academy of Microbiology (AAM) and a Fellow of the American Association for the Advancement of Science (AAAS). His group was previously supported by the Spastic Paraplegia Foundation (SPF) under the award entitled "Molecular mechanisms and small-molecule targeting of atlastin", which partially funded research of a former PhD student, Dr. John O'Donnell. The current, SPF-funded project "Extrinsic regulation of atlastin and its HSP variants" supports Ms. Carolyn Kelly in her graduate studies.

The Sondermann laboratory is interested in the inner workings of cells, the building blocks of the human body, and how defects in cellular processes may contribute to disease. In this SPF-supported project, the group studies a fundamental process, the fusion of cellular membranes that define a central transport and sorting hub in the cell, the so-called endoplasmic reticulum. Changes in this process due to mutations in specific genes have been associated with Hereditary Spastic Paraplegia (HSP) and Hereditary Sensory Neuropathy (HSN). Specifically, disturbance of the process through defective proteins made from the mutated genes affects the development and function of neurons including those that innervate the lower limbs, leading to early-onset gait disorders. One such protein that is often found altered in spastic paraplegia (i.e. subtype 3A) and that safeguards cellular structure is called atlastin, an enzyme that uses chemical energy to fuse cellular membranes in the endoplasmic reticulum.

In previous work, the Sondermann group used molecular approaches to study the structure of the intact atlastin protein and of its defective forms that are causative agents of HSP. By determining their three-dimensional structures ("shape") and studying their exact mode of action, Dr. Sondermann and his group contributed to our basic understanding of the mechanisms that maintain neuronal function and how mutations break the underlying processes. Such detailed information may help in the development of strategies to correct or balance defects due to atlastin's improper function in HSP.

The recent award funds an extension of the project that takes on another dimension. Like in mechanical devices, which are assembled from many pieces that work together to conduct a specific task, cells are composed of many individual proteins that act together to ensure proper function. Individual proteins rarely work alone, but instead assemble into bigger complexes and/or are subject to regulation by reversible modifications. It is likely that disease-causing mutations also alter these modes of assembly and regulation, which would inform on the mechanisms in cells that underly the development of disease. This area of research is uncharted territory for atlastin proteins, despite the fact that these proteins are so fundamental for the cell and an organism. In preliminary work, they identified such modifications and assemblies for atlastin, which provides a parts list of a molecular machine that protects neuronal function. With support by the SPF, they now propose to shed new light on the inner working of this machine and its control of cellular function. A particular question they pursue is whether (and how) HSP-associated mutations in atlastin impact the machine's mode of operation.

Diagnosing and fixing a defective machine requires a detailed understanding of its parts and how they work together. The same is true for a defective cell – the discovery of the processes that lead to improper function has the potential to aid in diagnosis, prognosis, and therapy in the future.

Dr. Hiroshi Mitsumoto

Dr. Hiroshi Mitsumoto is the Wesley J. Howe Professor of Neurology at Columbia University at The Neurological Institute of New York and NewYork-Presbyterian Hospital/Columbia University Medical Center. He received the Donald C. Mulder Award for achievement, leadership, and dedication in ALS from ALS Association in 1996. In 1998 he became the 5th recipient of the Forbes Norris Award from the International Alliance of ALS/MND Associations for his "compassion and love of humanity in the study, management or support of ALS/MND". In 2000 he received the Lou Gehrig Memorial Award from the MDA.

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In May 3rd & 4th, 2019, The Spastic Paraplegia Foundation was one of the main sponsors of the second International **Primary Lateral Sclerosis** Medical Conference in Philadelphia, PA. The previous International PLS Medical Conference had been in Santa Cruz, CA in 2004. It had also been supported by The Spastic Paraplegia Foundation.

The top PLS experts in the world were invited and attended this 2019 conference and over 30 attended. Several people with PLS as well as the SPF president were in attendance. Dr. Mitsumoto began the Conference with an introduction and history of PLS science back to 1865 when Charcot described it as "hysterical attacks of limb contracture and sclerosis of lateral column and atrophy of anterior roots."

Christina Fournier, MD from Emory University, who the Spastic Paraplegia Foundation supported in her educational grant, spoke about the cross sectional PLS Registry. It is comprised of 233 patients at 20 NEALS sites. Lenard van den Berg from Utecht Univ spoke about PLS in the Netherlands. Albert Ludolph, Univ of Ulm, spoke about PLS in Germany. John K. Fink, MD, Univ of Mich, spoke about the difference between PLS & HSP. Terry Heiman-Patterson, Temple Univ, talked about the difference between PLS & ALS. Martin Turner, Oxford University, talked about the Mills variant. Jennifer Murphy, UCSF, talked about cognitive and behavioral impairment with PLS. Edward Huey, Columbia Univ, talked about similarities and differences from other types of cognitive/behavioral impairment (AD, PD, ALS, HD, ET). Matthew Kierman, Univ Sydney, talked about cortical excitability. Seth Pullman, Columbia Univ, talked about Transcranial Magnetic Stimulation (TMS). TMS is an objective marker of upper motor neuron dysfunction in PLS. TMS quantifies corticospinal tract involvement with PLS. Kourosh Rezania, Univ Chicago, talked about the very strong correlation of the assessment of a shared neural drive. Zachary Simmons, Penn State, spoke about what EMG changes constitute "no Lower Motor Neuron involvement" in PLS?

Martin Turner, Oxford University, talked about PLS neuroimaging and functional insights. He showed many images of PLS changes to the brain that are not found in ALS. Peter Bede, Trinity C. talked about overlapping and distinctive imaging signatures in PLS and ALS. Sabrina Paganoni, MGH, who received an educational grant from The Spastic Paraplegia Foundation, spoke about glial activation in patients with PLS assessed with [11C]-PBR28 PET. Georg Haase, INSERM, talked about Motor Neuron Subsets in ALS and PLS: from development to degeneration. Madison Gilmore, Columbia U, talked about the novel PLS Functional Rating Scale (PLSFRS) which is a 68 point PLS progression measurement. Lauren Elman, U Penn, and Suma Babu, MGH, talked about quantitative Upper Motor Neurological Scale. Pat Andres, Formerly MGH, spoke about quantitative motor performance. Giovanni Manfredi, Weill-Cornell Univ, spoke about Mitochodrial bioenergetics. This is a great discriminator between ALS & PLS. Estella Area-Gomez, Columbia U, spoke about Lipidomics. There are changes in many categories of lipids. Lipidomics analysis of serum discriminates ALS & PLS.

The next day, Teepu Siddique, North Western Univ, spoke about Sporadic PLS and familial PLS. Dr. Siddique talked about genetic pleiotropy and pathologic pleiotropy which was first described by Jean-Martin Charcot 1825-1893. Phillippe Corcia, Univ Tours, talked about PLS in familial ALS. Guy Rouleau, McGill University, talked about genes for familial PLS. TMEM175 is also involved in Parkinson's disease. Matt Harms, Columbia Univ, talked about an exome and genome sequence study. Dr. Ian Mackenzie, Univ British Columbia, talked about the neuropathological and biological view on PLS, ALS and FTD. Dale Lange, HSS, and Jim Wymer, Univ Florida, talked about Symptomatic Treatment: Dalfampridine trial. Dalfampridine has been very effective with MS. It increases walking speed and leads to an improved quality of life. Their goal is an increase of 20% in walking speed. Hiroshi Mitsumoto, Columbia U, talked about whether we are ready for a PLS clinical trial of a disease-modifying treatment. They need a sensitive scale, a good biomarker, a goal attainment scale, time to fail, a natural history study of PLS, a multi site study, a patient registry and better diagnosis criteria. There were then several large panel discussions of topics such as The PLS Diagnostic Criteria, An International PLS Registry and Where do we go from here?

Overall, this 2nd International PLS Medical Conference proved to not only allow the top PLS experts in the world to share very important information about PLS but also to ignite a strong energy and commitment among these scientists to work together in a new very concerted effort to find a cure or treatment for PLS.

These studies continue to draw us so much closer to the day when we can announce that a cure or treatment has been found and people with HSP and PLS may be cured. How wonderful that day will be when we can tell over 100,000 people worldwide that their suffering has ceased. When that day arrives in the not so distant future, you will know that it was only because of your generous support that we have reached our goal. Thank you again!

Sincerely,

Frank Davis

SPF President

Would you like more information about us?

The Spastic Paraplegia Foundation, Inc. ("SPF") is a not-for-profit corporation that is a United States & Canada, volunteer-run, health organization dedicated to funding cutting-edge scientific research to discover the causes and cures for Hereditary Spastic Paraplegia and Primary Lateral Sclerosis, and to diminishing suffering by education and support.

The SPF home corporate office is located at 1605 Goularte Place, Fremont, CA 94539-7241. A copy of our latest annual report or financial statement may be obtained by writing to this same address or calling 877-773-4483.

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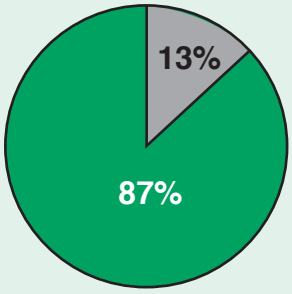
Where your dollars go



87% Mission

13% Management and Administration

REVENUE	2018	2017	2016
Donations	$736,884	$545,375	$544,866
Team*W*alk	36,275	37,789	40,741
Special Events	15,500	17,500	40,401
Program Fees & Products	47,957	27,700	20,343
Investment Income	10,869	2,420	150
Total Support and Revenue	**$816,485**	**$630,784**	**$646,521**
DIRECT EXPENSES			
Management and Administration	102,491	78,934	61,091
Program Expense	58,387	57,408	54,674
Mission	**87%**	**87%**	**91%**
Management and Administration	**13%**	**13%**	**9%**
Total Expenses	**$160,878**	**$136,342**	**$115,765**
NET ASSETS *(as of December 31)*	**$648,858**	**$892,614**	**$321,192**
GRANTS PLEDGED	**$584,000**	**$900,000**	**$697,250**

The Board of Directors continues to maximize your donations as 87% of each dollar raised supports the foundation's mission of research, information and support. The majority of Program Expenses are the costs of holding our Annual Conference which brings hundreds of people with HSP & PLS together with the world's leading HSP & PLS scientists for knowledge, support and fellowship. These costs are mostly offset by Program Fees and Corporate Sponsorships.

Management and Administration which are valuable and necessary foundation expenses are services which are donated to the foundation. Legal, accounting, income tax preparation, management and medical grant review services are all provided at zero cost but are recorded for tax purposes. We are pleased to report that a total of $854,0000 has been approved for research funding for 2019. This is made possible by the continued support of our generous donors. 2018 was highlighted by the Match My Gift program. Over $425,000 was raised as the result of anonymous donor matches. Our heartfelt Thank You goes out to you for your continued support.

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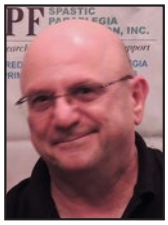

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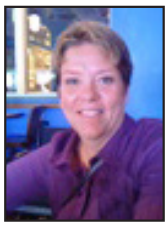

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