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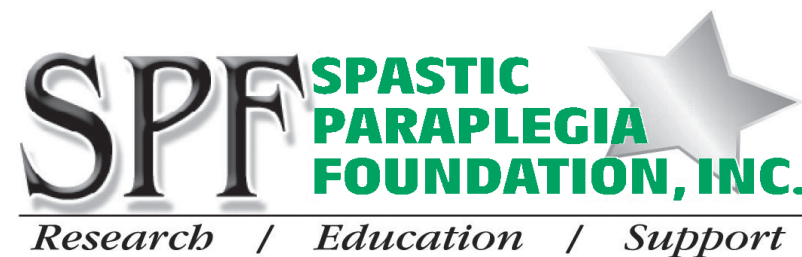
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ANNUAL REPORT

## STEPPING FORWARD TODAY TOWARD A CURE TOMORROW

### President's Letter



Dear Friend,

I want to again thank you for your past donations because they are making a cure for HSP and PLS seem so much more within reach. 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

Dr. Allan Mackay-Sim and associates at Griffith University, Brisbane, Australia, created olfactory stem cells from SPG4, SPG7 and control patients. They then differentiated these stem cells into forebrain neurons. Both SPG4 & SPG7 forebrain neurons were determined to have slower peroxisome trafficking and were much more prone to oxidative stress. Peroxisomes are involved in the breakdown of very long chain fatty acids, branched chain fatty acids, D-amino acids, and polyamines, Dr. Mackay-Sim, then, individually applied the two drugs nescapine and epathilone D and both drugs alleviated these symptoms. They are still pursuing a mouse HSP study with these two drugs. They are also in the process of making movies of the peroxisome trafficking in HSP and control cells with and without these two drugs to further back up their findings.

Dr. Jonathan Rios, with the Scottish Rite Hospital in Dallas TX, ran a study to evaluate and improve personalized genomic medicine for people with Hereditary Spastic Paraplegia. While they have determined that there does not seem to be a dramatic

increase in the rate of children being diagnosed with HSP beyond what they achieved with targeted genetic testing methods, they were surprised to find several cases where the clinical whole exome sequencing provided alternative diagnoses to HSP with similar symptoms. It has also provided them with enough information to identify several variants of unknown significance (VUS). Further study of these VUS could determine why the same gene can cause either complicated or uncomplicated HSP depending on the variant. They have identified several new potential HSP genes and a variant that is predicted to block the normal function of the protein it encodes. This sort of loss-of-function variant is extremely rare. They went on to further show how this variant alters where the protein accumulates in the cell. The position of this protein, known to regulate nerve and brain development, is critical for its function. This approach has also identified a new variant within a well studied gene that is critical for nerve development. They have resequenced this gene in additional HSP subjects and identified several very rare variants that may also be associated with HSP. They are currently testing whether this variant alters nerve activity.

Jordan Inloes and Benjamin Cravatt, with the Scripps Research Institute in San Diego, CA, studied the principal triglyceride hydrolase lipid metabolic enzyme DDHD2, the mutation of which, is the cause of a very rare form of HSP, SPG54. The function of normal DDHD2 is to reduce brain lipid droplet accumulation. Mutated DDHD2 causes an accumulation of lipids in the brain leading to a thin corpus callosum with cognition, vision and speech problems.. They experimented with mice and have almost thoroughly come to the conclusion that eliminating the proteins DGAT1 and DGAT2 allowed for brain lipid droplets to not accumulate and could serve as a cure for SPG54. Further study is necessary to support their conclusion.

Continued next page.

### *President's Letter continued*

Holger Sonderrmann, with Cornell University in Ithaca NY, studied two atlastin isoforms, alt1 and alt3, the mutation of which is a cause of some forms of HSP. They have developed and refined their study of atlastin's intrinsic molecular mechanism which has allowed them to describe alt1's mode of action at an unprecedented level of detail and also compared discrete steps in the biochemical cycle between ATL1 and ATL 3 isoforms. They determined several new structures for the ATL 1 and ATL 3 catalytic core fragment, a module that is affected by many HSP mutations. The hypothesis they are working with is that the HSP atlastin mutations are defective in the GTPase-Dependent switching mechanism. The GTPase mechanism is necessary for the movement of proteins through membranes and the transport of vesicles within the cell. Dr. Sonderrmann's research is now in the position to pinpoint the exact steps in the catalytic cycle that distinguishes the mutant atlastin from its normal counterpart.

Dr. Evan Reid and his associates at The Cambridge Institute for Medical Research in the United Kingdom, studied how the defects in endoplasmic reticulum (ER) endosome contacts impact lysosome function, or the cell's internal cleaning function, in people with HSP. The ER is a network of membranous tubules within a cell involved in protein and lipid synthesis and they need to be periodically removed for normal cell function. Contacts between endosomes and the endoplasmic reticulum (ER) promote endosomal tubule fission to allow for their removal. Dr. Reid and associates found that the interaction between the microtubule severing enzyme spastin and the ESCRT protein IST1 at ER-endosome contacts drives this endosomal tubule fission. Failure of their fission causes disrupted lysosomal enzyme trafficking and abnormal lysosomal formation. There are two forms of spastin, M1 and M87, and they seem to serve a redundant function to rescue tubule fission. This explains why the vast majority of, if not all, spastin disease mutations affect both isoforms of the protein. Similar lysosomal abnormalities were seen in cellular models lacking strumpellin or REEP1. Mutations in spastin, strumpellin or REEP1 cause different forms of HSP. Their results implicate that it is the failure of the ER-endosome contact process that leads to the failure of nerves to function and suggests that the coupling of ER mediated endosomal tubule fission to lysosome function links different classes of HSP proteins into a unifying pathway for axonal degeneration. Their work potentially links many classes of HSP proteins previously considered functionally distinct, in a unifying pathway of HSP pathogenesis that incorporates all of the most common HSP subtypes.

In 2015, Dr. Tobias Ulmer with the University of California in Los Angeles discovered that CPT1C mutation is the cause of SPG73 HSP. He determined that CPT1C localizes to the endoplasmic reticulum, is expressed in motor neurons and interacts with atlastin-a, an endoplasmic reticulum protein encoded by the ATL1 gene known to be mutated in pure HSPs. The CPT1C mutation alters the protein conformation and reduces the lipid droplets in primary cortical neurons. The association of the CPT1C mutation with changes in lipid droplet biogenesis supports a role for altered lipid-mediated signal transduction in HSP pathogenesis. In this paper he writes that he hypothesizes "this point mutation to enhance CPT1C catalytic activity which compromises axonal health in the corticospinal tract." He is currently in the process of trying to crystallize CPT1 for further analysis.

## *\$900,000 in New Promising Research*

The Spastic Paraplegia Foundation issued \$900,000 in new research grants earlier this year. Each grant is for a two year period. The Chair of our SPF Scientific Advisory Board, Martha Nance, summarized our 2018 research by saying "the caliber of these proposals are excellent and speak to a bright future for HSP and PLS research".

Dr. Sabrina Pananoni MD, PhD with Harvard University was given the highest ranking by our Scientific Advisory Board. "This project aims to capitalize on a promising pilot study (funded by SPF) that resulted in evidence of a specific pattern of neuroinflammation in patients with PLS, suggesting a distinct pattern from ALS and HSP....The project has direct application to clinical diagnosis of HSP and PLS and potential utility in clinical trials as a biomarker."

Dr. Peter W. Baas PhD with Drexel University has worked for many years on HSP research. He has a top lab with an excellent track record in the field of HSP. His current project is entitled: "Functional Basis of SPG-4 based hereditary spastic paraplegia". Dr. Baas will be examining regeneration after amputation in mouse cortical neuronal cultures to answer the question whether HSP in SPG4 is due to SPG4 not being fully functional or whether, when mutated, confers new or enhanced activity on the protein. He will then examine the effect of potential therapeutic drugs in these cell systems.

*Continued on other side*



Dr. Gerardo Morfini, PhD, with the University of Illinois will be investigating the role of M1 spastin versus M87 spastin, whose function to date has been thought to be primarily redundant on axonal transport, a cellular process critical for the maintenance of upper motor neuron connectivity. His research team will also evaluate mechanisms underlying activation of the protein kinase CK2 by M1 spastin. Preliminary evidence suggests this protein kinase may represent a novel therapeutic target to treat SPG4 HSP.

Dr. Mimoun Azzouz, PhD, ERC Advanced Investigator, Chair of Translational Neuroscience, Deputy Head, Neurology Unit Director of Research and Innovation, Sheffield Institute for Translational Neuroscience, Sheffield University, United Kingdom, is targeting his research specifically on SPG15 Gene Therapy. Dr. Azzouz promises to make great strides for this particularly rare, HSP disorder.

Dr. Giovanni Stevanin, PhD's project at Institut du Cerveau et de la Moelle épinière in Paris, France, involves the identification of the neuronal transcriptomic signature associated with lysosomal defects in HSP SPG11. Dr. Stevanin is bringing together two expert teams, one in pathology that brings the relevant animal model and working hypothesis and the second team that is expert in RNA studies and has improved single cell micro dissection and analysis. They have recently revealed a pathogenic link of HSP SPG11 with lipid metabolism. SPG11 is the most frequent autosomal recessive spastic paraplegia. Patients suffer from motor impairment, spasticity, weakness and mental

impairment. The aim of his study is to identify the pathways involved in the physiopathology of SPG11 using an extensive transcriptomic analysis. This study could very well lead to new treatments for patients with SPG11.

Finally, we are supporting the research of Dr. John Fink, MD, with the University of Michigan, who also serves as our SPF medical advisor. Our SAB reviewers wrote: "Enthusiasm for this proposal is thus driven by the investigator and the significance of the problem to be addressed." Dr. Fink will characterize the serum miRNA profile of 20 PLS, 20 ALS and 20 healthy individuals and identify differentially expressed miRNAs. This is a very important research area because of the lack of an available test to confirm the diagnosis of PLS and identification of a reliable biomarker will further our understanding of the disease pathogenesis and suggest novel therapeutic targets.

These studies continue to draw us so much closer to the day when we can announce that a cure or treatment has been reached and people with HSP and PLS may be cured. How wonderful that day will be when we can tell over 100,000 people world wide that your 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



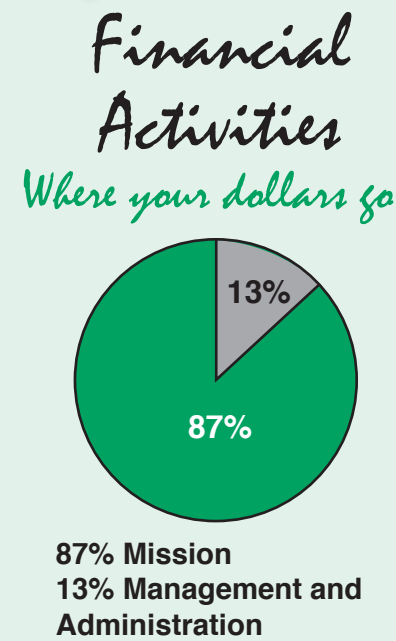


Would you like more information about us?

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.



REVENUE	2017	2016	2015
Donations	\$545,375	\$544,866	\$465,462
Team Walk	37,789	40,741	30,739
Special Events	17,500	40,401	52,222
Program Fees & Products	27,700	20,343	17,009
Investment Income	2,420	150	202
<b>Total Support and Revenue</b>	<b>\$630,784</b>	<b>\$646,521</b>	<b>\$565,634</b>
DIRECT EXPENSES			
Management and Administration	78,934	61,091	106,391
Program Expense	57,408	54,674	42,002
<b>Mission</b>	<b>87%</b>	<b>91%</b>	<b>81%</b>
<b>Management and Administration</b>	<b>13%</b>	<b>9%</b>	<b>19%</b>
<b>Total Expenses</b>	<b>\$136,342</b>	<b>\$115,765</b>	<b>\$148,393</b>
<b>GRANTS PLEDGED</b>	<b>\$900,000</b>	<b>\$697,250</b>	<b>\$615,955</b>
<b>NET ASSETS</b>	<b>\$892,614</b>	<b>\$321,192</b>	<b>\$487,686</b>

(as of December 31)

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 \$900,000 has been approved for research funding for 2018. This is made possible by the continued support of our generous donors. 2017 was highlighted by the Match My Gift program. Over \$403,000 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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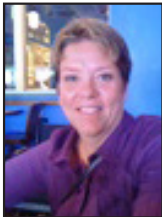
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