SPF SPASTIC PARAPLEGIA FOUNDATION, INC.

Research / Education / Support

2013 ANNUAL REPORT

STEPPING FORWARD TODAY TOWARD A CURE TOMORROW

President's Letter

Dear Friends,

With the generous help of thoughtful supporters like you, 2013 was a huge step forward for The Spastic Paraplegia Foundation. PLS & HSP research is progressing so fast, Dr. John Fink with the University of Michigan Medical Center said "it is just exploding". The day when we can joyfully announce a cure or treatment is stepping ever closer. Our sincere and heartfelt thanks goes out to the SPF community at large and to all of our generous supporters (Page 6) for making this possible.

Many of the expert speakers at our Annual Conference last June in Saint Louis, MO. updated us on the research generous donors like you have allowed us to support. Dr. John Fink said that a new HSP study is now being published about every three days and a PLS study every 15 days. He said "optimism is really rational!"

Dr. James McNew with Rice University spoke about the cellular aspects of HSP. He explained the discoveries they are making on the function of the different HSP genes in the cellular interactive process and the Spastin and Atlastin proteins in the malfunctioning cell.

Dr. James Berry explained what is being accomplished in the joint projects that SPF and North East ALS Consortium (NEALS) are working together to accomplish. He said the knowledge of motor neuron diseases is "growing rapidly". NEALS is in the process of training more clinical researchers about HSP and PLS to create a much larger scientific community on Upper Motor Neuron disorders.

The Virginia Freer Sweeney Clinical Research Training Fellowship grant that SPF received in 2012 was granted to Christina Fournier, MD. Dr. Fournier is studying at Emory University and making dynamic progress in PLS research. She is conducting a multi-center clinical trial for patients with PLS by identifying both eligible research subjects and NEALS investigators to participate in research efforts. She is also leading an effort to expand the NEALS HSP & PLS disease database to not only capture additional patients, but also collect longitudinal and historical data.

Stepping forward toward a cure, The Spastic Paraplegia Foundation is diligently working with our distinguished international Scientific Advisory Board to concentrate and refine our research efforts. We are working on developing an extensive patient registry. Our SPF State Ambassador Program is expanding to reach out to those few states that are currently not represented. We are reaching out through social media, our Synapse Newsletter and our web site (sp-foundation.org) to ask more people with HSP & PLS to join our data base so we can be prepared when Clinical Trials begin.

This is a very hopeful, exciting time for The Spastic Paraplegia Foundation and it is only possible because of donors like you. Thank you so much.

Sincerely,

Frank Davis

SPF President

CHASING A CURE

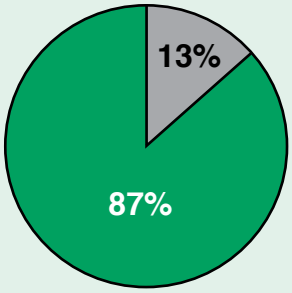
Would you like more information about us?

The Spastic Paraplegia Foundation, Inc. ("SPF") is a Massachusetts not-for-profit corporation that is a nationwide, 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 4 Couture Rd., Southampton, Ma 01073. A copy of our latest annual report or financial statement may be obtained by writing to the SPF at 4 Couture Rd., Southampton, Ma 01073, or calling 877-773-4483.

Financial Activities

Where your dollars go



87% Mission
13% Management and Administration

REVENUE	2013	2012	2011
Donations	$443,304	$231,010	$232,424
Sweeney Fellowship	0	338,548	0
Team*Walk*	53,436	112,710	45,575
Special Events	59,584	130,269	174,555
Program Fees & Products	12,021	16,795	11,066
Investment Income	90	143	11
Total Support and Revenue	**$568,435**	**$829,475**	**$463,631**
DIRECT EXPENSES			
Fundraising	$30,736	$50,646	$66,688
Management and Administration	41,704	39,408	39,943
Program Expense	28,225	39,040	17,449
Total Expenses	**$100,665**	**$129,094**	**$124,080**
GRANTS PLEDGED	**$800,000**	**$370,000**	**$600,000**
FELLOWSHIP	**N/A**	**$200,000**	**N/A**
NET ASSETS	**$1,041,869**	**$1,131,046**	**$430,341**

(as of December 31)

The Board of Directors continues to maximize your donations as 87% of each dollar raised supports the foundations mission of research, information and support. In addition, over half of the management and administrative expense consists of web and printed material costs. Other major costs include the annual audit fee, license filings in multiple states and bank credit card fees.

Professional fees which are valuable and necessary foundation expenses are services which are donated to the foundation. Legal, accounting, income tax preparation and medical grant review services are all provided at zero cost.

We are pleased to report that a total of $800,000 has been approved for research funding for 2014. This is made possible by the continued support of our generous donors. 2013 was highlighted by the addition of the Match My Gift program. Over $195,000 was raised as the result of anonymous donor matches. Our heartfelt Thank You goes out to them.

Research Review

The Spastic Paraplegia Foundation, since being founded in 2002 has funded over $4,000,000 in research toward the cures of Hereditary Spastic Paraplegia and Primary Lateral Sclerosis. Here is just a sample of some of the progress made in 2013:

Spartin Regulates Synaptic Growth and Neuronal Survival by Inhibiting BMP-Mediated Microtubule Stabilization

The authors studied the spartin protein, which is deficient in 40% of patients with SPG20 HSP, to discover how it causes neuronal degeneration. Using a spartin-deficient fruit fly model they discovered that the spartin protein is present at the neuromuscular junction, where the end of the nerve cell makes contact with the muscle. Spartin prevents nerve cells from excessive stimulation, reducing the sensitivity of the nerve cell to signals coming from the muscle cell. In spartin-deficient flies, the neuromuscular junctions are excessively overgrown.

The brains of spartin-deficient flies contain much higher levels of a particular form of the protein alpha-tubulin which can form microtubules. In spartin-deficient flies, this excessive formation of microtubules is harmful to nerve cells. They found that the microtubule-destabilizing drug vinblastine prevented this overgrowth and reduced programmed cell death.

These findings suggest that at the cellular level, SPG20 has similarities with other forms of HSP. NIPA1 (SPG6), atlastin-1 (SPG3A), and spastin (SPG4) have previously been found to be involved in the same signalling process at the neuromuscular junction, all protecting nerve cells from overstimulation.

Nahm M, Lee MJ, Parkinson W, Lee M, Kim H, Kim YJ, Kim S, Cho YS, Min BM, Bae YC, Broadie K, Lee S.

Neuron. 2013 Feb 20;**77**(4):680-95. doi: 10.1016/j.neuron.2012.12.015.

A Spastic Paraplegia Mouse Model Reveals REEP1-Dependent ER Shaping

The authors developed a mouse model to study REEP1 deficiency found with SPG31 HSP. The authors discovered that REEP1 is particularly expressed in upper motor neurons and is a membrane-linked protein found to be associated with the synthesis of lipids and proteins. The Endoplasmic Reticulum is a membranous network of sac-like structures in most cells. In REEP1-deficient mice, neurons of the primary motor cortex had fewer, but longer endoplasmic reticulum segments.

Reference was made to atlastin-1 and spastin. These proteins are involved in linking the endoplasmic reticulum to the microtubule network. Reticulon 2, mutated in SPG12, is also mentioned as an endoplasmic associated and shaping protein.

The authors speculate whether Layer V motor neurons might require a particularly elaborate endoplasmic reticulum in order to maintain their axons, which are extremely long

Beetz C, Koch N, Khundadze M, Zimmer G, Nietzsche S, Hertel N, Huebner AK, Mumtaz R, Schweizer M, Dirren E, Karle K N ,Irintchev A, Alvarez V, Redies C, Westermann M, Kurth I, Deufel T, Kessels MM, Qualmann B, Hübner CA.

J Clin Invest. 2013 Oct 1;**123**(10):4273-82. doi: 10.1172/JCI65665. Epub 2013 Sep 24. PubMed PMID: 24051375; PubMed Central PMCID: PMC3784524.

An ESCRT-Spastin Interaction Promotes Fission of Recycling Tubules from the Endosome

The authors studied spastin, which is defective in SPG4 HSP. Spastin is essential to enable certain proteins to be returned to the plasma membrane. In spastin-defective cells, many cell-surface proteins are incorrectly routed and degraded when they should be returned to the cell surface. This normal recycling of proteins to the cell surface takes place via recycling tubules that depend on spastin, necessary for microtubule severing, to be released. These unreleased proteins are eventually degraded by lysosomal enzymes. Spastin-defective cells thus are lacking many of the proteins that normally would be present on the cell surface, including receptors important for axonal signaling and survival. Spastin shares its involvement in fission of endosomal tubules with strumpelin, which is deficient in SPG8.

This study makes a major contribution in our understanding of the cell biological and biochemical impact of deficiencies in spastin, and suggests why spastin is required for the health of the longest axons of the corticospinal tracts.

Allison R, Lumb JH, Fassier C, Connell JW, Ten Martin D, Seaman MN, Hazan J, Reid E.

J Cell Biol. 2013 Aug 5;**202**(3):527-43. doi: 10.1083/jcb.201211045. Epub 2013 Jul 29. PubMed PMID: 23897888; PubMed Central PMCID: PMC3734076.

- A Saudi Arabian team discovered a gene that, when mutated, causes a juvenile onset form of PLS.
- Dr. Mary Kay Floeter at the National Institutes of Health in Virginia described disease progression compared to changes in motor neurons' axons.
- Teams in England and Italy found cellular differences between PLS and ALS patients who were experiencing cognitive issues.
- Additional progress continues to be made using diffusion tensor MRI as a diagnostic tool to distinguish PLS from ALS earlier than current methods.
- A study published in the January 31, 2014 issue of *Science Magazine*, revealed how an international team led by scientists at the University of California, San Diego School of Medicine report doubling the number of known causes of Hereditary Spastic Paraplegia. They generated what they called an "HSP-ome" or how each of the HSP causes link together and even how they relate to other more common neurodegenerative disorders such as Alzheimer's Disease and Amyotrophic Lateral Sclerosis (ALS). "This is very exciting since identifying the biological processes in neurological disorders is the first step toward the development of new treatments," said co-lead author Ali G. Fenstermaker. "We identified several promising targets for development of new treatments."

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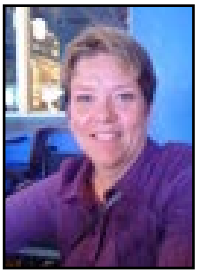

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