SPF SPASTIC PARAPLEGIA FOUNDATION, INC.

RESEARCH | EDUCATION | SUPPORT

2022 ANNUAL REPORT

MOMENTUM

STRENGTH OR FORCE GAINED BY MOTION OR BY A SERIES OF EVENTS

Greg Pruitt

Dear SPF Supporter,

I want to share with you how energized and encouraged we are as we prepared the 2022 Annual Report! We are seeing tremendous momentum, growth, and outreach at the SP-Foundation. We appreciate every contributor at every donor level, every volunteer who serves on our SPF Committees, every member of the Board of Directors, our Scientific Advisory Board, our doctors, and researchers, as well as every new member of our population willing to be part of our work and mission to find treatments and cures for HSP and PLS. We are gaining great and increasing momentum toward that goal. All of you are a very important and necessary part of our team!

The most recent financial information provided by SP-Foundation Treasurer David Lewis is just one more indication of the increasing momentum. According to his numbers, donations to SPF increased from 2020 ($880,546) to 2021 ($1,1,08,397), a staggering one-year increase of 26%! But you all worked collectively to maintain and increase that momentum in 2022. You raised $1,193,850 in total donations, another 8% increase! This kind of continued work is so important and necessary to make the research possible.

You will find in this Annual Report information on our current research projects. Please take the time to read and familiarize yourself with these projects. We set out to summarize as simply as possible so that we non-researchers can better understand the research work being done for all of us. We must constantly push ourselves to keep going, keep moving, and keep achieving new things. Your SP-Foundation Board of Directors at the Annual Conference in St. Louis, MO, has agreed to fund and work with a group of doctors and researchers to establish nine centers of excellence locations. These locations will help establish the critical infrastructure, including a shared clinical database, biobank, genome database and enable testing key elements in pilot projects. The doctors/researchers and SP-Foundation Board collectively believe this a very important step toward clinical trial readiness, moving these rare diseases more quickly toward significant funding and working with agencies like the National Institute of Health and pharmaceutical companies.

Again, Thank You All! Every dollar and every minute of work you can contribute is an important part of continuing to increase SP-Foundation momentum! We need it to constantly push ourselves to unlock our greatest potential. Stay focused and committed to raising HSP and PLS Awareness and keep the momentum going to help us reach 2023 fundraising goal of $1.5 million!!

Best Always,

Greg Pruitt

SPF President

RESEARCH AND DEVELOPMENTS

An increased focus on our diseases is timely and critical. There is indeed reason to hope for treatments and therapies in coming years that will restore significant function to people affected by HSP and PLS and other related diseases. Uncovering more of the riddles is leading to important findings for related conditions such as ALS, spinal cord injury and Alzheimer's Disease. Researchers say common threads link the many neurologic conditions that affect millions of people. Read more about the important research on SP-Foundation.org.

Peter Bede, M.D., Ph.D.

Peter Bede, M.D., Ph.D

Professor in Neurology, Trinity College Dublin

www.tcd.ie

Characterising Infratentorial Pathology In PLS

Existing imaging studies of PLS overwhelmingly focus on supratentorial brain changes, despite the crucial contribution of spinal and brainstem pathology to the symptoms of PLS. One of the most striking gaps in the research literature of PLS is the paucity of dedicated spinal cord, cerebellar and brainstem studies. While postmortem studies have invariably described bilateral pyramidal tract degeneration in the spinal cord with the relative preservation of the spinal cord gray matter as a distinctive, disease-defining feature, this has not been adequately studied in vivo to date. Novel MRI techniques now permit the non-invasive quantitative measurement of spinal cord, cerebellar and brainstem changes, and crucially, these changes can now be tracked accurately over time in longitudinal studies. The main objective of this proposal is therefore the systematic characterisation of progressive spinal cord, brainstem, and cerebellar disease burden in PLS and establishing the clinical correlates of the identified infratentorial changes.

Marka van Blitterswijk, M.D., Ph.D.

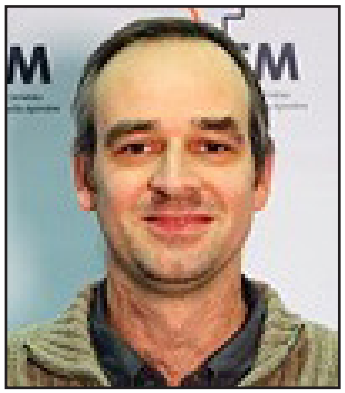
Marka van Blitterswijk, M.D., Ph.D.

Associate Professor of Neuroscience & Associate Consultant II (ACII)

Genomics of ALS & Integrative Analytics (GAIA), Mayo Clinic Florida

Revealing Determinants Of PLS With Long-Read Sequencing Drivers Of PLS

Dr. Marka van Blitterswijk's laboratory, at Mayo Clinic Jacksonville, studies the causes of neurological diseases, including primary lateral sclerosis (PLS). PLS is a relentlessly progressive disease that results in the loss of specific types of cells, which are called upper motor neurons. Support from the Spastic Paraplegia Foundation, Inc., will allow Dr. Van Blitterswijk and her team to create a wealth of data for patients with PLS. She will use innovative techniques to study brain tissue from patients with PLS, assisting her to unravel what is going on in the brain of these patients. By comparing patients with PLS to patients with related disorders as well as control subjects, she hopes to find potential drivers of the disease. As such, this project could aid in uncovering relevant processes, which may help to decipher the underpinnings of PLS. They will also identify factors that might influence the disease, and could be used as urgently needed biomarkers, and/or point to possible treatments.



Frederic Darios, Ph.D.

Alexandra Durr, M.D., Ph.D, Pu-PH.

Frederic Darios, Ph.D.

Principal Investigator, Ph.D., CR1, INSERM

Alexandra Durr, M.D., Ph.D., PU-PH

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ICM-Paris Brain Institute

Institut du Cerveau – ICM, Hôpital Pitié Salpêtrière

Modulation Of Mitochondrial Function As A Modifier Of SPG4 Physiopathology

Hereditary Spastic Paraplegia (HSP) due to mutations in the SPAST/SPG4 gene is characterized by high clinical variability, notably of age at onset. Using a large cohort of SPG4 patients with either early or late age at onset, they identified a gene modifying age at onset, SARS2 that encodes a mitochondrial protein. Their objective is to investigate how SARS2 can modulate the evolution of SPG4 symptoms. This project will help understand the role of a modifier gene in disease variability, which is crucial for prognosis and genetic counselling. Elucidating its mechanisms of action may elucidate physiopathological pathway that may help with the development of therapeutic strategies in the future.

Jonathon Howard, Ph.D.

Jonathon Howard, Ph.D.

Eugene Higgins Professor of Molecular Biophysics & Biochemistry, Professor of Physics, Quantitative Biology Institute, Yale University

Functions Of Alternative Isoforms Of Spastin In Vitro And In Vivo

Spastin is a member of a family of microtubule-severing ATPase enzymes that play key roles in restructuring the cytoskeleton during many cellular processes such as mitosis, ciliogenesis, cell migration, neurodevelopment and cell-wall biosynthesis in plants. Mutations in the spastin gene in humans are the major cause of HSP, but the etiology of the disease, such as the associated progressive gait disorder and degradation of motor axons – is poorly understood. Part of the reason is that spastin is a complex, multifunctional protein. A shorter isoform is soluble and cuts microtubules; paradoxically, it also promotes their growth. A longer isoform is membrane-associated and tethers to organelles, but its enzymatic activities are not known. The goal of this grant is to explore the activity of the long isoform through two aims: in vitro studies with purified proteins and in vivo studies using a model organism for studying neuronal development. In the first aim they will purify the long isoform and use state-of-the-art microscopy techniques to study its membrane binding and its interaction with microtubules. These studies will elucidate the biochemical properties of the long isoform. In the second aim, they will test the role of the two isoforms in disease by introducing disease mutations into fly neurons, which are model systems for studying the

development of the nervous system. The expected outcome of this proposal is a detailed model of the mechanism of spastin-dependent microtubule severing and growth, including the role that membrane binding plays in spastin activity.

Roberta La Piana, M.D., Ph.D.

Roberta La Piana, M.D., Ph.D.

Montreal Neurological Institute, McGill University

Identifying New Imaging Diagnostic Criteria In Hereditary Spastic Paraplegias (HSPs).

This research study aims to identify and characterize the presence of white matter abnormalities in HSPs that can be used as imaging biomarkers of disease progression and for future therapeutic trials. The involvement of the brain white matter is frequently documented in many neurogenetic disorders, and it often represents crucial imaging criteria to orient the diagnostic process of affected subjects. HSPs are among the neurogenetic conditions in which white matter involvement is most frequently observed. However, in most forms, white matter abnormalities have not been investigated further and their role as potential imaging biomarkers has not been explored.

With their study they will: 1) perform MRI pattern recognition of white matter involvement in HSPs to identify novel imaging diagnostic criteria, and 2) map brain white matter microstructural abnormalities in HSPs to disclose future disease progression biomarkers.

Emanuela Piermarini, Ph.D.

Emanuela Piermarini, Ph.D.

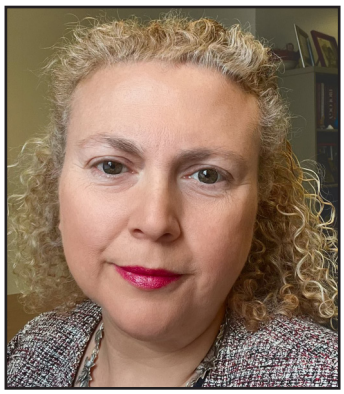
Research Scientist, Drexel University College of Medicine

Gene Therapy Approach For SPG4-Based Hereditary Spastic Paraplegia

SPG4-based Hereditary Spastic Paraplegia (HSP-SPG4), caused by mutations of the SPAST gene, is the most diagnosed form of HSP. Researchers have been working to understand the mechanisms underlying the disease so that they can develop mechanism-based therapies. However, the best therapy, at least in theory, is to turn off the expression of the mutant spastin and replace it with the expression of wild type spastin. Such a therapy would theoretically succeed regardless of mechanism and could be extended to other forms of HSP as well. Dr Piermarini's proposal deals with the preclinical issues that must be addressed before this approach can be used on patients. The proposed research, if successful, will provide effective therapy to people suffering from HSP-SPG4. To do so, 1) she will test the gene therapy vector on cultured cells and make potential adjustments to the vector based on the results. 2) she will test the vector on the HSP-SPG4 mouse model by assessing behavioral gait parameters and the impact on axonal degeneration.

CHASING A CURE

P. Hande Ozdinler, Ph.D.



P. Hande Ozdinler, Ph.D.

Associate Professor, Department of Neurology

Northwestern University, Feinberg School of Medicine

Faculty, Chemistry of Life Processes Institute

Faculty, Les Turner ALS Center

Faculty, Cognitive Neurology and Alzheimer's Disease Center

Faculty, Robert H. Lurie Comprehensive Cancer Research Center

Investigation Of NU-9's Impact On Diseased HSP Upper Motor Neurons In Vitro

Dr. Ozdinler, in collaboration with Dr. Silverman found that NU-9 improves the health of upper motor neurons that are diseased due to misfolded SOD1 toxicity and TDP-43 pathology, by improving the integrity of mitochondria, endoplasmic reticulum, by reducing protein aggregation and by improving cytoarchitectural stability. Since these problems are shared with the upper motor neurons diseased in HSP and PLS diseases, Dr. Ozdinler is now going to utilize in vitro techniques to study precise cellular response to NU-9 treatment.

It is Essential to Register with the Spastic Paraplegia Foundation!

Medical researchers contact SPF to locate people with a specific gene mutation. Upon request, we provide a list indexing people with a specific gene mutation from the SPF database. If you are registered, then you may be selected for medical research or gene therapies.

Join at SP-Foundation.org/news-resources/stay-informed.html

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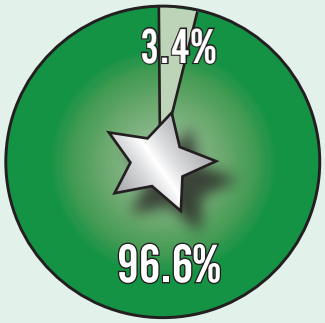
Where your dollars go



96.6% Mission

3.4% Management and Administration

REVENUE	2022	2021	2020
Donations	$1,193,850	$1,089,032	$947,749
Team*W*alk	0	19,365	35,011
Special Events	N/A	N/A	N/A
Program Fees & Products	31,365	0	45,803
Investment Income	-63,725	29,866	10,729
Total Support and Revenue	**$1,161,490**	**$1,138,263**	**$1,039,292**
DIRECT EXPENSES			
Management and Administration	39,225	30,260	86,125
Program Expense	125,547	63,652	63,508
Mission	**96.6%**	**97%**	**92%**
Management and Administration	**3.4%**	**3%**	**8%**
Total Expenses	**$164,772**	**$93,912**	**$149,633**
NET ASSETS *(as of December 31)*	**$1,001,687**	**$1,115,751**	**$851,834**
GRANTS PLEDGED	**$1,015,189**	**$771,000**	**$888,904**

**Financial Information provided by SP-Foundation Treasurer, David Lewis.*

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SPF SPASTIC PARAPLEGIA FOUNDATION, INC.
RESEARCH | EDUCATION | SUPPORT

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Join the SP-Foundation Mission!

The Spastic Paraplegia Foundation, Inc., (SP-Foundation) is a not-for-profit corporation with membership from all over the world. SP-Foundation is the only organization in North America dedicated to finding cures for both HSP and PLS. SP-Foundation is a volunteer-run health organization providing trusted, accurate, and up-to-date information. The primary mission of SP-Foundation is sponsoring scientific medical research for finding commonalities, causes, treatments, therapies, and cures for Hereditary Spastic Paraplegia and Primary Lateral Sclerosis. Any amount you contribute supports scientific investigators with "seed-grant awards". SP-Foundation utilizes the work of committees focusing on specific goals and implementation strategies as an outreach for Fundraising, Marketing, Education and Ambassadors. Consider your personal skills, talents, and interests, then engage them by joining a committee in our mission to find a cure.

The SPF home corporate office is located at 6952 Clayborne Drive, O'Fallon, MO 63368-6202. A copy of our latest annual report or financial statement may be obtained by writing to this same address or calling 877-773-4483.