

Synapse

Volume 21, Issue 2 Spring 2018

Newsletter of the Spastic Paraplegia Foundation

Letter from the President



Dear SPF Community,

As I write this, it is about a week before Easter and the first day of Spring. This is the time of the year when several religions observe what many call the secret to life. What is that secret? It's one of those secrets hidden in plain sight. It's also one

of those secrets that can trouble the soul, so we often turn away from it or close our eyes to it. It is that, often loss is necessary before we can have a renewal. The Jews who went through Passover, had to leave their homes and travel for 40 years before they found their promised land. The Christians had to watch their leader suffer and die the most humiliating death possible before Easter morning could ever happen.

Jesus said, "Unless a grain of wheat falls into the earth and dies, it remains just a single grain; but if it dies, it bears much fruit" (John 12:24). What is it about loss that is necessary for our lives to become better? It's the pattern of loss and renewal that runs throughout our lives and our world. Even if you've never thought of this as the secret to life, you've lived and experienced it, sometimes by choice and other times by chance. Either way it's there.

And you've got to know that dying is about more than our physical death. Yes, it is that, but it's also more than that. We die a thousand deaths throughout our lifetime. The loss of a loved one, a relationship, health, opportunities, a dream; all deaths we didn't want or ask for. Other times we choose our losses and deaths. We give up parts of ourselves for another. We change our beliefs and values so that we can be more authentically ourselves. And sometimes there are things we need to let go of, things we cling to that deny us the fullness of life we want: fear, anger or resentment, regret and disappointment, guilt, the need to be right, approval.

Many of us in the rare disease community are very familiar with loss. HSP and PLS are by definition a loss that is despairingly progressive. I can't speak for anyone else but

it is often difficult for me to see the positive side of having HSP. I know that the loss has resulted in my having a whole new way of life that is not nearly as difficult as I had thought it would be when I was first diagnosed. This progressive dis-ability is helping me learn about my abilities. I have gained many new very valuable friends and acquaintances in my different roles with this Foundation.

Many of you are willing to experience a personal loss when you donate to The Spastic Paraplegia Foundation. I hope you do so, knowing that there will be an incredible renewal of a cure for HSP and PLS in the future. Yes, the major gains are still to be experienced for most of us. Imagine the day when people all over the world with HSP and PLS experience the cure of their and/or their loved ones' condition from the research we are so painstakingly supporting.

But you also know that you don't plant a seed and go back in ten minutes or the next day and see a new sprout. Growth can be slow and the fruit of new life takes time, usually longer than we want it to. Yet, even when unseen, unbelieved, or unrecognized, the power is present and at work in the depths of our life, in the dark and hidden places. That's the mystery of life.

I want to thank you again for being willing to make your donations to The Spastic Paraplegia Foundation. Our Board of Directors just recently appropriated \$900,000 of your hard-earned donations to support the research that our expert Scientific Advisory Board recommended to us from the absolute best of the hundreds of research proposals we have received. Please know that your donations are a very worthy investment in the future for over 100,000 people worldwide with HSP and PLS. Please remember that there will be a glorious renewal or cure/treatment that I so look forward to celebrating with you in the not so distant future!

All the Best,

Frank Davis
Frank Davis, President

How to Help

We operate out of the strength of our community, caring friends and sponsors. Your help makes a difference!

Please contact us at volunteer@sp-foundation.org to help in one of the areas below or to suggest another way you can get involved.

Support Research to Speed Our Cures by Volunteering

Below you'll find information on some of the ways you can help SP Foundation in their search for a cure to PLS and HSP.

Raise Funds: The primary focus of SPF is to raise funds to support research to find the causes, treatments and cures for Hereditary Spastic Paraplegia and Primary Lateral Sclerosis. Our major fundraising activity consists of a TeamWalk. Individuals can help organize local fundraisers. People are also needed to secure corporate sponsorships and help with grant applications.

Patient Connection Programs: Organizing a Connections gathering for people to meet, share stories and help one another is a great service. Events can be as simple as meeting for coffee! In areas with large patient populations, SPF seeks to establish Chapters.

Conference Organizers: The SPF seeks event coordinators in or near metropolitan areas who can work with us to organize Conferences for our community. These events feature speakers and programs on special topics of interest to our community as well as provide the opportunities for individuals to meet others. Conferences can be half-day or full-day events.

Communications: Individuals with writing, research, website or graphic design skills are needed to assist with various communication initiatives.

Ambassadors: Ambassadors raise awareness about our disorders as well as enhance community building and industry relationships. You can assist with media relations, share your story, speak at local groups or help with grassroots advocacy.

Business and Administrative Support:

Volunteers with business and administrative skills can play a valuable role in administering the work of the SPF. Most of the help is coordinated through email correspondence and uses popular Office applications.



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The Spastic Paraplegia Foundation Inc. (SPF) is a national, not-for-profit, voluntary organization. It is the only organization in the Americas dedicated to Primary Lateral Sclerosis (PLS) and Hereditary Spastic Paraplegia (HSP).

Synapse Editors

John Staehle.....Senior Editor
Malin Dollinger, M.D..... Medical/Research Editor

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Spastic Paraplegia Foundation
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information@sp-foundation.org
or www.sp-foundation.org

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SPF Medical Advisor:

John K. Fink, M.D., University of Michigan

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Board Business

Highlights from SPF Board of Directors meetings held between December 2017 and February 2018

December

Giving Tuesday & Fundraising (Frank Davis): Our goal was \$10,000 and we received between \$13,000 and \$16,000! This is a big jump from last year's total. YTD for all giving is \$491,000. We are behind last year's total at this time, but we have not yet received this year's significant donations from anonymous donors. If we delete those contributions from last year's total, we are actually ahead of 2016.

Dr. Fink's Last Monthly Patient Meeting (Jackie Wellman): Jackie attends the meeting by invitation via a conference call. At the meeting, Dr. Fink said that most people with HSP will progress for years but will then plateau. This is a recent observation and he is working on understanding why this happens.

Board Special Election (Frank Davis): Jim Sheorn has reapplied to join the board. The Board passed a motion to increase the size of the board by one person. The Board then passed a motion to add Jim Sheorn to the Board of Directors.

Invitae (John Cobb): This was a continuation of a discussion started at last month's meeting. John proposed SPF start the process of joining Invitae's Patient Insights Network™. This action will attract researchers to our Foundation. Greg Pruitt, Norma Pruitt, Mark Weber and John have all been involved in discussions about this. Mark was impressed with the cost to the SPF - \$0! John moved that we pursue a relationship with Invitae. The motion passed. *[Editor's Note: See related article, "Invitae Expands Network of Patients in Rare and Ultra-Rare Diseases," elsewhere in this issue.]*

January

Annual Conference Strategic Planning (Norma Pruitt): Norma would like to have someone speak on the Scientific Advisory Board the conference. She and Mark Weber will discuss this before the next Board meeting. On January 15th hotel reservations and conference registration will be opened. Greg Pruitt added there will be discounts for those who register early.

Synapse Report (written by John Staehle, Editor): Content for the Winter issue of Synapse was uploaded to the printer, Gulf Business Printing, on January 7th. Several of the articles were submitted by new authors who responded to my call for articles, the first time it actually yielded material from new authors since I started editing the newsletter in 2014. The call for articles for the Spring issue will be made the middle of February. This issue will feature the Annual Conference including speakers' photos and bios, a registration form, conference sponsors, and more. There will also be an article on gene therapy and its ethical issues plus one on the product lifecycle of prescription drugs.

February

Annual Conference Strategic Planning (Norma Pruitt): Norma is continuing to work on the agenda. Would like to include a way to honor SPF's major donors at the Annual Conference, though some donors may not want to be identified. More discussion on this will be part of the March meeting agenda. We don't want to offend any of the major donors, but we do want to show our appreciation.

Synapse Report: John Staehle: The Winter issue was completed January 15th and authorization was given to the Gulf Business Printing to print and mail almost 2,000 copies. The issue's PDF file was also posted on the website. The call for articles for the Spring issue was sent out on February 10th.



Ahoy Matey, All Hands Hoay!



Registration is open for the 2018 Spastic Paraplegia Annual Conference Pittsburgh, PA June 22-23, 2018. Join us to meet new friends, learn about the latest in scientific medical research and share strategies for living with Hereditary Spastic Paraplegia and Primary Lateral Sclerosis.

The Spastic Paraplegia Foundation coordinates the world's largest annual Spastic Paraplegia gathering – the Annual SPF Conference. For two days, conference attendees meet to learn from world-leading researchers and clinicians, to network, to reunite with old friends and to make new ones. Many people, from patients to caregivers to medical professionals, travel from all over the world to attend the conference. The location moves each year, providing a broader opportunity for people to attend and travel. Accessibility accommodations are kept in mind when planning and choosing conference locations. Attendees have the opportunity to learn about spastic paraplegia relating to research, genetics, physical therapy, living with HSP and PLS, coping, caregiving, and more.

Sessions at the conference will include the process of selecting researchers who receive scientific and medical research grants from the SP-Foundation. Researchers and doctors will share information about their work, updates on gene therapy, and CRISPR genome editing. We will include breakout sessions for just men, just women, and just children in which each group can talk with each other about daily personal living issues. If you have a concern or a question that you would like to submit ahead of time, please

let us know, and we will address it during the breakout session.

There will be informative sessions on clinical research and related disorders for therapeutic development, CReATe Consortium, human genetics and neurology. John Fink, MD, who serves as the SP-Foundation's scientific medical advisor and is the Director of the Neurogenetic Disorders Clinic at the University of Michigan and Physician Scientist at the Geriatric Research Education and Clinical Center will speak and take questions on Saturday afternoon. Additional speakers include Corey Braastad, PhD, Dale J. Lange, MD, Hiroshi Mitsumoto, MD, DSc, Sabrina Paganoni, MD PhD, Jeffery Statland, MD, Stephan Züchner, MD, PhD, and others. We will also recognize the State Ambassadors and Donors at the conference. There will be a special program for the children in the hotel courtyard.

Please register early to receive the best conference discounts by going to the SPF website, <https://sp-foundation.org.presencehost.net>, or by completing the registration form at the end of this newsletter. The hotel is accepting reservations by calling the **PITTSBURGH AIRPORT MARRIOTT at 412-490-6604, located on 777 Aten Rd., Coraopolis, PA 15108**. There is free parking, complimentary airport transportation and free Wi-Fi. Mention "SPF" for a discounted room rate of \$102 and let them know what time you need the handicap shuttle to pick you up at the airport.

Yo! Ho! Ho! We will be pirating a course to Find a Cure, Raise Funds, and Participate in Research. We look forward to seeing you in Pittsburgh.

See Ya Soon,
Norma and the Conference Planning Committee

2018 SPF CONFERENCE SCHEDULE

FRIDAY, JUNE 22

All Sessions held in Main Conference Room, unless otherwise noted

Registration 11:30 AM – 6:00 PM

AFTERNOON

Welcome & Introductions

Frank Davis, SPF President, Tim Croghan, MC

SPF Scientific Research Grant Process

Mark Weber, Esq.

Invitae's Patient Insights Network Registry

John Cobb, SPF

PLS Research Updates

Sabrina Paganoni, M.D., Ph.D.

BREAK

Importance of Nutrition & Stretching

Sara Azarius Eichmiller, Iyengar Yoga Institute (includes children)

Updates on Gene Therapy

Corey Braastad, Ph.D.

BREAKOUT SESSIONS

MEN: Greg Pruitt, Moderator

WOMEN: TBD, Moderator

CHILDREN: Lauren Braastad, Moderator

Welcome Reception (Cash Bar)

Dinner (Served)

SATURDAY, JUNE 23

All Sessions held in Main Conference Room, unless otherwise noted

Breakfast (Served)

MORNING

Welcome Back

Frank Davis, SPF President, Tim Croghan, MC

CRaTe Consortium

Jefferey Statland, M.D.

Tackling PLS

Hiroshi Mitsumoto, M.D., D.Sc.

Therapies, Impaired Mobility and Ampyra Trial

Dale J. Lange, M.D.

Human Genetics and Neurology

Stephan Züchner, M.D., Ph.D.

Lunch (Served)

AFTERNOON

State Ambassadors Recognition

Tina Croghan, SPF

HSP and PLS

John K. Fink, M.D.

Open Forum Discussion

Questions & Answers

John K. Fink, M.D.

Conference Wrap-Up

Tim Croghan, MC

Social Mingle at Hotel Cash Bar (On Your Own)

Sponsor & Donor Reception

CHILDREN'S PROGRAM

Children's Program located in Hotel Courtyard, unless otherwise noted

FRIDAY AFTERNOON

Welcome and Introductions

Activity 1: Exotic Bird Show

SNACKS & BREAK

Importance of Nutrition &

Stretching – Join parents in the Main Conference Room

Children's Breakout Session,

Breakout Room in Conference Center

SATURDAY MORNING

Welcome & Introductions

Activity 2: Puppet Show

BREAK

Activity 3: Balloon Artist

LUNCH PARTY & BREAK

SATURDAY AFTERNOON

Activity 4:

Activity 5:

SNACKS BY THE FIRE PIT

Join Parents in the Main Conference Room

Sponsor & Donor Reception



10th Annual Conference Presenters



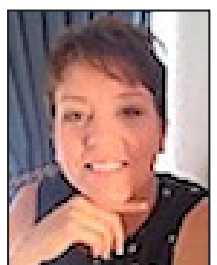
Corey Braastad, Ph.D., is the Vice President and General Manager of Genomics at Covance Drug Discovery, part of LabCorp. Dr. Braastad has completed training, performed research, and developed programs in clinical trials, pharma research support and clinical genetic

diagnostic products. Dr. Braastad is a published author who has many years of experience in senior team leadership, lab operations, and R&D. He is a member of the board of directors for the Spastic Paraplegia Foundation and Cure SMA. He is also a Member of The Human Variome Project, the American Society of Human Genetics, the American College of Medical Geneticists, the American Academy of Neurology, the American Society of Cell Biologists and the Radiation Research Society. He has a Ph.D. in Molecular and Cellular Biology and Biochemistry from Brown University School of Medicine and a B.S. in Biology - Magna Cum Laude from the University of Massachusetts at Dartmouth.



John Cobb was elected to the SPF Board in May of 2013. He is from Alexandria, VA and graduated from the College of Charleston in 2009 with a Bachelor of Science in Economics before entering the Financial Services Industry. After three years with Morgan Stanley he

transitioned to Edelman Financial Services, a financial planning firm headquartered in Fairfax, VA. He now works with their Business Intelligence team as a data analyst in Berkeley, CA. John was diagnosed with HSP in early 2003 and is the second in his family with the condition. He has successfully organized and conducted three golf tournament fundraisers benefitting SPF.



Tina Croghan is a retired teacher who still stands by the motto that she greeted each student as they entered her classroom with, "What we learn with pleasure, we never will forget." With a Master of Arts in Theatre and a Master of Fine Arts in Directing from Lindenwood University – St.

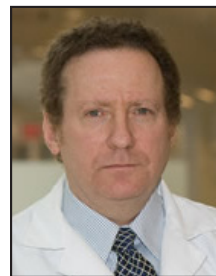
Louis, Tina uses her performance and people skills to inform, advocate and fundraise for the Spastic Paraplegia

Foundation. Tina has HSP and was clinically diagnosed in late 2002. She has since received her genetic diagnosis of SPG7, and now looks forward to upcoming patient drug trials. Tina has been part of the SPF family since 2006 and has been the Annual Conference Chairperson for 2009 & 2013 (St. Louis) and 2016 (Chicago). She was a member of the conference planning committee for the 2017 conference in Atlanta and is again part of the 2018 planning committee for the Annual Conference in Pittsburgh. Tina became a member of the SPF Board in 2012 and has continued her efforts in finding a cure for HSP & PLS. Tina lives in O'Fallon, Missouri with her husband, Tim, and her support dog, Thunder.



Sara Azarius Eichmiller is Western Pennsylvania's most experienced teacher of Iyengar Yoga. She has been teaching yoga full-time for over 20 years and has developed Pittsburgh's only Iyengar Yoga studio to cultivate a community of teachers and students dedicated to the Iyengar method.

Sara's credits include three years as President of the Yoga Training Association of Pittsburgh, Yoga Coordinator at the River's Club fitness facility, Director and Founder of Shadyside Yoga and Director and Owner of Yoga On Centre. She has instructed over forty of Pittsburgh's yoga teachers in her teacher education programs and ongoing mentorship program. Sara's teaching is a direct approach to yoga asana, pranayama, philosophy and meditation. Sara graduated in 1990 from Penn State University with a degree in print journalism. She worked for five years in Pennsylvania as a newspaper photographer before living in North Carolina and Texas and beginning her training in yoga.



John K. Fink, M.D., is the Director of the Neurogenetic Disorders Clinic at the University of Michigan, Ann Arbor. He's also a Professor in the university's Department of Neurology and is a Physician Scientist at the Geriatric Research Education and Clinical Center, Ann Arbor Veterans

Affairs Medical Center. His research interests are analysis of inherited and degenerative disorders of the nervous system (including hereditary spastic paraplegia, primary lateral sclerosis, inherited movement disorders, schizophrenia) and regulation of neuronal development.

Dr. Fink received his M.D. from the Medical College of Ohio in Toledo. He did his residency training in neurology and genetics at the University of Virginia, Charlottesville. At the National Institutes of Health in Bethesda, Maryland, he did a post-doctoral fellowship in the Developmental and Metabolic Neurology and Medical Genetics departments.



Dale J. Lange, M.D., is the Chairman of Neurology and Neurologist-in-Chief at Hospital for Special Surgery and Professor of Neurology at Weill Cornell Medicine in New York City. His entire career has been devoted to caring for patients with neuromuscular disease. The focus of his research has

been to seek better ways to diagnose and discover new treatments for patients with motor neuron and related diseases. He has been and is the principal investigator of multiple clinical research projects involving novel therapies that are both investigator-initiated and industry sponsored. Dr. Lange received his medical degree from New York Medical College and completed his internship in medicine at Albany Medical Center. He was a resident in neurology at Tufts New England Medical Center in Boston, MA. He was the clinical Fellow of the Muscular Dystrophy Association at the Neurological Institute at Columbia University College of Physicians and Surgeons.



Hiroshi Mitsumoto, M.D., D.Sc., is a Wesley J. Howe Professor of Neurology at Columbia University Medical Center and the Director of the MDA/ALS Clinical Research Center since 1999. In 1968, he graduated from Toho University School of Medicine, Tokyo. Beginning in

1972, he pursued further medical and neurology training at Johns Hopkins University, Case Western Reserve University, Cleveland Clinic, and Tufts University. In 1983, he began working at the Cleveland Clinic as the Director of the Neuromuscular Section and ALS Center. He has since been involved with extensive research in ALS, including improving patient care/management and end of life issues, multiple clinical trials, biomarker development, and multisite epidemiological studies. He organized several large national and international ALS Conferences and is currently updating and developing the new International ALS Clinical Trial Guidelines. He has published more than 170 articles in peer-reviewed journals, mostly in ALS, in addition to reviews, chapters,

and books. For more than a decade, his research interests have expanded to PLS.



Sabrina Paganoni, M.D., Ph.D., is an Assistant Professor at Harvard Medical School and Staff Physician at Massachusetts General Hospital (MGH) and Spaulding Rehabilitation Hospital. She obtained her M.D. degree at the University of Milan in Italy and a Ph.D. in Neuroscience at

Northwestern University (Chicago, IL). She completed her medical training in Boston (residency in Physical Medicine & Rehabilitation at Spaulding Rehabilitation Hospital and fellowship in EMG/Neuromuscular Medicine at Brigham and Women's Hospital/Massachusetts General Hospital). She is Board-certified in Physical Medicine & Rehabilitation, Neuromuscular Medicine and Electrodiagnostic Medicine. She is currently working at MGH in the Amyotrophic Lateral Sclerosis (ALS) clinic. She is faculty at the MGH Neurological Clinical Research and her research focuses on ALS and PLS therapy development. Dr. Paganoni was supported by the SPF with a 2-year fellowship that allowed her to foster a community of researchers interested in PLS. She is site Investigator of one PLS clinical trial and two PLS observational trials and leads the NEALS PLS Registry. Dr. Paganoni is using novel neuroimaging techniques as pharmacodynamic biomarkers for clinical trial development. She is also passionate about developing innovative assistive technology tools that can improve quality of life for people with ALS and PLS.

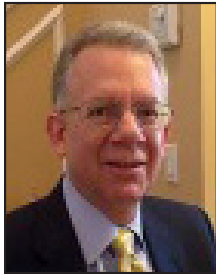


Jeffrey Statland, M.D. is an assistant professor of neurology at the University of Kansas Medical Center with both clinical and research training in neuromuscular diseases. His primary research interest is in FSHD, one of the most prevalent adult muscular dystrophies. Recent

advances in our understanding of the genetic mechanism behind FSHD have led to the identification of potential therapeutic targets, resulting in a pressing need to develop sensitive, disease-relevant outcome measures for clinical trials. The University of Kansas Medical Center is a clinical site for CReATe. The Clinical Research in ALS and Related Disorders for Therapeutic Development (CReATe) Consortium will enroll patients with sporadic and familial forms of amyotrophic lateral sclerosis,

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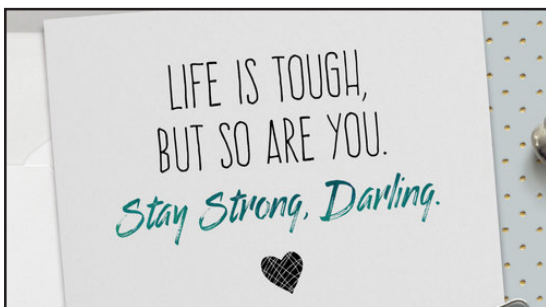
frontotemporal dementia (FTD), primary lateral sclerosis (PLS), hereditary spastic paraplegia (HSP), and progressive muscular atrophy (PMA). The goals of the CReATe consortium are to advance therapeutic development for this group of neurodegenerative disorders through study of the relationship between clinical phenotype and underlying genotype and also through the discovery and development of biomarkers.



Mark Weber, Esq., is one of the co-founders of the SPF and was its first president. He serves as the SPF's legal counsel and chairs its research grant committee. Mark is an attorney and served for eleven years as a prosecutor in Massachusetts. He is currently in private practice in Connecticut concentrating in child abuse and neglect cases. Mark has been diagnosed with HSP. He lives with his wife, Andrea, in Sherman, Connecticut, and has a son in college.



Stephan Züchner, M.D., Ph.D., is a Professor and Chair for the Dr. John T. Macdonald Foundation Department of Human Genetics. He is a trained neurologist and molecular geneticist with research interests in identifying genetic variation associated with disease. His lab has identified several genes for Mendelian neurodegenerative disorders and also evaluated risk factors for complex genetic conditions, including Alzheimer disease, Parkinson disease and obsessive-compulsive disorder. His lab is amongst the pioneering groups that have promoted genome sequencing methods for disease gene identification in humans, mice, and drosophila. He is currently pursuing large-scale exome and genome analysis in multiple neurodegenerative disorders and developing innovative new software tools that allow real time-shared analysis of large amounts of genomic data.



10th Annual Conference Leaders



Frank Davis, SPF President, frank.davis@sp-foundation.org, Frank was President of Pittman and Davis, a direct marketing catalog company specializing in the sale of gift packages of fresh fruit and other perishable gift food items before his retirement. From 2005 to 2011, Frank served as secretary for the Board of Directors. He was elected president in January of 2012. He holds a bachelor's degree in both business administration and sociology from Trinity University and a master's degree from Southern Methodist University. Frank has HSP and lives in Harlingen, Texas.



For the last eleven years, **Tim Croghan** has been a dedicated supporter of the Spastic Paraplegia Foundation. Along with his wife, Tina (an SPF Board Member), they focus all of their attention in advocating and raising funds to advance the research efforts to find a cure for HSP and PLS. Tim has continued using his communication skills in assisting with the operation of the SPF Annual Conferences in St. Louis (2009 & 2013), Chicago (2016) and Atlanta (2017). Tim will again be the Master of Ceremonies at the 2018 Annual Conference. He is excited about seeing everyone this June in Pittsburgh.



Please consider making a gift to the Spastic Paraplegia Foundation in your Will and Financial Plan.

Spastic Paraplegia Foundation 2018 ANNUAL CONFERENCE PITTSBURGH, PA

JUNE 22-23, 2018

**Pittsburgh Airport Marriott
777 Aten Road, Coraopolis, PA
(412) 490-6604**

Conference Sponsors

KRIS BROCCINI



Kris was diagnosed with PLS at UCSF in June 2003. After looking up PLS on the internet, she found the SPF and made plans to attend the Lexington, MA, Conference and TeamWalk in late September 2003 where she and her family were welcomed with open

arms. Questions were answered, stories were compared and a whole new world to think about was discovered. Frightening but informative. She thinks everyone needs to attend that first conference. Kris served on the SPF Board of Directors from 2007 to 2016. Her personal support of the SPF Annual Conference for the past 8 Conferences is the result of remembering how she felt when she first found the SPF community.



INVITAE

Invitae, a genetic information company, is bringing genetic testing into

mainstream medical practice by providing high-quality, affordable genetic testing.



MNG LABORATORIES
Neurogenetic Answers™

MNG Laboratories™ provides expert diagnostics through clinical services, complex biochemical testing and sequencing. Our

Next Generation Sequencing panels are the most cost effective and comprehensive available, particularly for cellular energetics defects, muscular dystrophies, epilepsy, cardiomyopathy and intellectual disabilities.



Each patient with a rare disease is a patient who needs to be heard and who deserves to be treated. And that is why Saol Therapeutics exists. We bring therapies for these serious and often life-threatening conditions to market and to the life of the patient who desperately needs it. Addressing the needs of patients with rare diseases and underserved neurological conditions are our passion and focus at Saol. Supporting patients with high unmet needs by offering promising treatment options is what drives us.

General Interest

My Alternative to Golf

By Jim Brewi, SPF Co-Ambassador, South Carolina

I originally wrote an article for the Fall *Synapse* in 2012 after hearing from another member about a recumbent tricycle shown at the SPF conference in Northern Virginia. At the time I had just given up golf due to the progression of my PLS, which was devastating to me being a scratch golfer. I was looking for something I could still do safely outdoors.

I wasn't sure what to expect or how long I could still do it, but I went ahead and purchased the trike. It's been the best investment and a life saver! At first, I started out slowly, building up strength and learning how to ride the trike. Mine is an eight-speed direct drive, meaning you have to pause your peddling for a moment to shift gears. This is a change from normal bikes where you have to pedal to change gears and it took me a while to get used to it. It's great when you come to a stop - you can change gears to whatever level you need to get going again without having to pedal. Getting on and off safely hasn't been an issue either; the brakes lock and there is room by the handles to push yourself up.



Jim Brewi Out for a Ride

The trike I bought is the TerraTrike Rambler model because its seat is 17 inches off the ground, the highest of their models. I'm using a walker full time now and I leave it next to my trike so I can transfer on and off safely. I find it exhilarating to be out riding and enjoying the beautiful weather and scenery, not to forget the health benefits. Nobody knows I'm disabled – I'm just the guy riding that cool bike. The trike is very comfortable to ride, too. It's like riding around in a lawn chair! I'm in my 12th year of PLS and, believe it or not, since 2012 I have put over 5,000 miles on my trike and am still going strong! I live in South Carolina most of the year now so I am able to ride all year round.

You can find more information about TerraTrike models and their pricing at www.terratrike.com. You can also find used trikes by searching on-line.

My Experience as the Maine SPF Ambassador

by Jeff Stern

Almost six years ago, I was diagnosed with Hereditary Spastic Paraplegia. I think I've had it all my life, but it has only been in the past decade or so that it reached a threshold where it became noticeable in my daily activities.

The diagnosis was bittersweet. On one hand, in the month between testing and diagnosis my mind took flight and I imagined the worst: *What if I have ALS?!* I was relieved when it turned out to “only” be HSP. On the other hand, I was shocked, confused and depressed that I had this weird neurological disease that's (currently) incurable, that will inevitably worsen over time, and that no one in my family or circle of friends had ever heard of before.

Thank goodness for the Spastic Paraplegia Foundation! I read everything on the SPF website (as well as other listings that popped up when I googled “Hereditary Spastic Paraplegia”). It was reassuring to know I wasn't alone in dealing with this disease. I went back to the SPF website often. One time, I noticed the organization was looking for an “ambassador” for Maine. I inquired and it sounded promising. This was in the summer of 2013.

After I got over the initial shock of my diagnosis, I felt strongly that I didn't want to be a passive victim. One good strategy for dealing with HSP head-on would be to reach out to others in my state who may have been dealing with their own feelings of isolation and frustration. This turned out not to be as altruistic as it sounds because I think I ended up getting as much, if not more, out of my ambassadorship than other folks in our Maine HSP/PLS community! But I wouldn't realize this until later...

The best part of being an ambassador was conducting the lunch connections. Sometimes turnout at these gatherings was good, sometimes not so much. Everybody leads such busy lives these days. It was always a challenge to coordinate schedules. Regardless of turnout, though, I never failed to be impressed by the good humor, knowledge and high

spirits of participants. I learned so much and always came away feeling empowered. I feel like I've made lifelong friends throughout the state who I can talk to about anything, not just HSP and PLS.

These connections weren't pity parties. Sure, we all face the reality of dealing with HSP and PLS. Some people had a hard time getting from one end of the restaurant to the other. But no one felt sorry for themselves. Instead, we joked and enjoyed good fellowship. It was awesome to be with people who understand the challenges of living with these diseases. Presiding over these events, I felt tremendous pride.

I organized a few "give back" nights at local outlets of national restaurant chains like Applebee's and On the Border. It's hard to raise huge amounts of money this way but we did alright. The generosity of people in the community was astounding! Almost as important as raising money, I think, was the opportunity these events provided for public education through news articles, press releases and editorials. It's impossible to place a price tag on that.

One of my primary duties was to welcome new members of SPF who live in Maine. I did my best to reach out and let them know they are not alone. My attempt to form a Maine SPF "book club" fell flat on its face, but if I saw an interesting article or read a book that applied to our situation, like *Defining the New Normal: A Guide to Becoming More Than Your Diagnosis*, I would spread the word about it to my Maine SPF family. I did my best to answer people's questions. When I didn't know off the top of my head, which was often, I always got the information I needed from the folks at SPF. Linda Gentner, Jackie Wellman, and Frank Davis were my primary go-to people. They never disappointed.

Circumstances in my life forced me to resign my ambassadorship last summer. This was regrettable because I found being an ambassador tremendously rewarding. I would recommend it to anyone. It is a way of being proactive that doesn't take a lot of time.

Whoever came up with the concept of SPF ambassadors deserves major kudos...it was a brilliant idea! Our strength is becoming informed and working together to find a cure. We're all in this together. The ambassador program is a way to reinforce community in all 50 states. I hope someone steps up soon to be the new Maine ambassador and I pledge to do my best to support them!

Tina's Tip - Calories vs. Mobility

By Tina Croghan, Missouri State Ambassador, SPF Board Member

It is so easy to turn into the local Mickey Dees and order a #2 with a Diet Coke. I know! Been there. Done that! But...after a while, the calories start to add up.

As many of you know, the bottoms of my feet always hurt. I've tried many remedies—lotion, potions, pills. The latest thing I have been doing has really helped me manage and reduce the pain and I wanted to share with you what has worked for me.

We all know how hard it is with HSP to maintain a lighter weight. Because of our limited mobility, it is hard (impossible) to get in the necessary daily movement of 10,000 steps—pshaw!

I have found that the lighter I am, the less pounding and dragging of my feet there is. Don't get me wrong! I know weighing less won't make me walk normal again, but it does lighten the load.

For many years, I have been on a pre-packaged meal plan, plus scheduled workouts and almost constant stretching.

These are MY reasons:

- 1st It was just more convenient when I was teaching. I had really long workdays (12+ hours).
- 2nd As my HSP progressed and I slowed down, my weight increased, making it harder to move/exercise.
- 3rd I had to lose weight for my son's wedding last March. (Pure vanity - I wanted to dance at the wedding!)
- 4th I wanted to continue to lose weight to stay as light as possible so as I age, my movements will be easier.
- 5th But this is the main reason. I wanted to be prepared for any trial or test that becomes available. **I want to be ready!**

My meals come prepackaged and frozen. All I need to do is pop them in the microwave for a few minutes! This way I am assured of getting a well-balanced meal every time and NO COOKING INVOLVED! (I can't stand long enough to cook.)

There are many managed, pre-prepared meal companies out there. I use Jenny Craig and I enjoy having their personal consultant help me manage my calories.

There are many ways for us to control our caloric intake, so there is no need to "just go through the drive-thru" because it's convenient, fast and easy. This is MY tip!

My Home Exercise Program

By Jim Sheorn, Tennessee State Ambassador and SPF Board Member

Stretches

Stretches should be held for at least 20 seconds and performed 3-5 times, preferably twice a day!

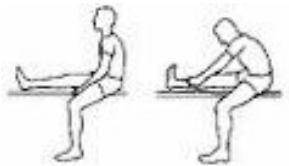
Hip Adductor Stretch: (inner thigh muscles). Standing – walk feet apart wide, can do a small lunge toward each side to isolate one hip more than the other. Sitting One-half Butterfly – on edge of bed or stair landing with one leg off and the other leg to be stretched is bent at the knee (one half butterfly position) push down on knee. I couldn't find a picture of this position, but it is similar to the "sitting hamstring stretch" below except the straight leg will be bent.



Hamstring Stretches: (back of thigh). Standing – bend forward at hips and try to touch your toes, keep knees straight! A modified version is to isolate one hamstring at a time.



Sitting: - on the edge of a bed or a stair landing with one leg off and the other leg to be stretched is straight at the knee, bend forward and try to touch toes.



Lying on Your Back - With the assistance of your spouse or exercise partner – you lie on your back with one leg stretched out in front of you and the leg to be stretched is hip flexed to 90 degrees. Press-up on lower leg to straighten knee (you may use a strap with this one as well).



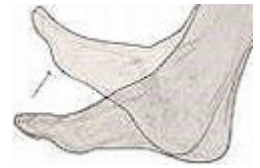
Calf Stretches: (back of lower leg). Sitting - wrap a belt or strap around forefoot and pull back on foot ("toes toward your nose"). Standing - place forefoot on a small object keeping heel on the ground, lean forward at hips.



Exercises

Exercises (strengthening exercises) are done in repetitions, building up to 30 at a time consecutively. When this becomes easy, you can increase the number of sets and/or use ankle weights to add resistance.

Ankles – Toe Raises: While sitting, bring toes up, moving them at the ankle and keeping the heel on the ground. One repetition is bringing your toes up and down. Do this exercise one ankle at a time or both together.



Knees – Knee Extension: While sitting on the edge of a bed or chair, straighten one leg at the knee and then return it to the bent position. Repeat! Switch to other leg and repeat the exercise.



Hips – Straight Leg Raises: While lying on your back, raise one leg up and then let it down, keeping your knee straight. After completing the number of repetitions you set as a goal, switch to other leg and repeat the exercise.



Hips – Abduction. Lying on your back and keeping your knee straight, move leg out and in (do not rotate hip outward, keep knee and toes pointed toward ceiling). Repeat with the other leg. Alternately, lie on your back with both knees bent and wrap a theraband around your thighs. Move both knees out and in. Lying on your side, raise top leg up and down keeping your knee straight and pointing forward. Repeat exercise using your other leg. Standing, "side-step" but do not compensate with your trunk!



Medical and Research

Gene Therapy: New Developments and Ethical Implications

By Malin Dollinger, M.D.

The Winter 2018 issue of *Synapse* contained an article describing the general principles of gene therapy, examples of early use to treat inherited diseases, and comments on its possible use in HSP and PLS. This article brings you up to date on newer research developments using gene therapy to treat a variety of genetic diseases and the important role of ethical considerations in deciding who to treat with gene therapy and whether such treatment is ethically sound and appropriate. You might find it beneficial to first review the previous *Synapse* article, since this article is a description of “what’s new and exciting,” and assumes you understand everything so far.

Thus far, gene treatments have mostly involved *somatic* cells, treating or replacing genes in the cells in our bodies that are diseased, in whom successful treatment helps us, the living. Presently, there are a very few attempts to genetically treat *germ* cells, the eggs and sperm that produce our offspring and our children’s future generations. Our abnormal “gene pool” would end with that type of treatment. That germline treatment, if successful in eliminating the HSP gene, might also produce unwanted mutations and other genetic diseases in all of our future descendants, not only in our children, but also our grandchildren, great-grandchildren, and so on, who, of course, do not have the opportunity to consent to this genetic manipulation since they have not yet been born or perhaps even conceived. This is a prime example of the role of ethics in deciding about gene therapy. Somatic gene cell therapy still is not intended to fix the germ cells. Thus, an abnormal gene could still be passed to future generations, even if the treated person has had “their” HSP, or inherited PLS, eliminated. There is also the remote risk of somatic gene cell therapy accidentally introducing the vector/new gene into eggs or sperm as well, thereby not only possibly fixing the HSP gene in future generations, but also introducing the risk of other diseases and abnormalities from that gene in future generations.

Gene therapy is a pathway to treat, cure and possibly even prevent diseases by changing or replacing a defective gene. We have 23 pairs of chromosomes in the nucleus of each cell in our bodies and each one contains

hundreds to thousands of genes. Genes are made up of DNA in long chains, arranged in a line called a double helix. The long line of genes on a chromosome is the same idea as a long line of different kinds of railroad cars hitched together to make a freight train. Genetic diseases have one or more abnormal chemical bases in the DNA chain, just like in a railroad train, where we might see an oil car substituted for a box car, or a flat car substituted for a coal car. Neither the railroad train nor the DNA can do its entire job correctly, but in the case of the human DNA, that abnormal place/substitution may cause a genetic disease. Some diseases, like sickle cell anemia, have a single wrong place in the DNA chain. Gene therapy helps by making a correction, by bringing that abnormal spot in the DNA back to normal, or perhaps eliminating it, since genes that don’t work correctly can cause disease. Gene therapy can replace or inactivate a bad gene or add a new gene that can help

fight disease. DNA is the same in every cell in our body, and contains the instructions, the “blueprint,” for telling RNA which protein to make, depending on where in the body that protein is needed. For HSP, the gene defect might involve the formation of nerves that function properly. However,

it is likely that HSP and inherited PLS may have more than one wrong place/error.

The website of the Spastic Paraplegia Foundation contains extensive scientific discussions of our neurologic disorders, HSP and PLS, and should be reviewed. In the most common form of HSP, SPG4 and now called SPAST, there are mutations in SPAST, which encode the microtubule-severing-spastin (which is inside our nerves). This form of HSP, SPG4, is caused by an abnormal *dominant* gene, so that acquiring the abnormal gene from either parent will cause the disease. A recessive gene requires a copy of the gene from both parents to cause the disease. Someone with only one recessive gene, from one parent, is called a “carrier.” They may not have the disease but can still transmit the disease to their children if the other parent is also a carrier (one chance in four).

A good example of a recessive gene is the disease sickle cell anemia, which is more common in African-American

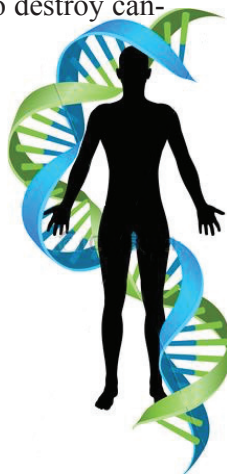


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cans. One abnormal gene on chromosome #11 causes one amino acid, glutamic acid, to be replaced by another, valine. This simple single substitution makes the red cells form long rods instead of small dishes. These rod-shaped red cells clog up the blood vessels. This disease is recessive, meaning one abnormal gene must be acquired from each parent, whereas most forms of HSP, SPG4/spastin in particular, are dominant and are caused from only one abnormal gene from one parent. Gene therapy would likely be much easier if only a single abnormal gene was the cause of a disease than it would be with multiple abnormal genes.

However, there is new evidence suggesting that in SPG4, diminished microtubule severing does not fully explain this disease. Microtubules are tiny hollow tubes within each cell, that are continually broken down and built up, and control critical cell functions, such as cell shape and cell movements. There are two variations of spastin (called isoforms), and the variation and effect of these different forms of spastin are much more complicated than a single abnormal gene and gene product. HSP in most cases is not simply one abnormal gene which produces one abnormal protein which interferes with how our nerves function. Gene therapy will thus not usually be simply the repair or replacement of a single HSP gene.

Gene therapy offers new hope for millions that are affected by diseases that are linked to genetic disorders like Hereditary Spastic Paraplegia (HSP), Primary Lateral Sclerosis (PLS) and ALS. However, gene therapy is being studied for a variety of other inherited/genetic diseases. These include blood diseases, such as sickle cell anemia and thalassemia, and various forms of cancer. A cancer example is the approval by the FDA of two pioneering treatments, Kymriah and Yescarta, that use the patient's own immune cells to fight rare types of cancer. These methods extract T lymphocytes, the cells that are part of the body's immune system, from patients. These T cells are then genetically changed to destroy cancer cells and injected back into the patient. This is called CAR-T therapy and these drugs are used to treat a rare type of bone marrow cancer and a type of lymphoma. One boy with a life-threatening skin condition had healthy skin stem cells removed, added copies of a healthy version of that gene, had more cells grown outside the body and then transplanted them back into the body as treatment [Germany].



In December 2017, the FDA approved the first gene therapy drug, Luxturna, for an inherited disease. Luxturna corrects a mutation that causes a retinal disease that makes people gradually go blind. This drug cures that blindness with a single \$850,000 injection into the eye. This very high cost is a practical as well as an ethical problem in using this drug. Scott Gottlieb, the FDA Commissioner, when announcing Luxturna's approval, stated, "Gene therapy will become a mainstay in treating, and maybe curing, many of our most devastating and intractable illnesses. We're at a turning point when it comes to this novel form of therapy." As you may quickly realize, there is a scientific and ethical balance between risks and benefits and asking an affected person if they would risk side effects in return for not going blind, their answer to that ethical question is easy.

Hemophilia-A is a blood-clotting disorder and people with this condition are called "bleeders." A new gene therapy that replaces the faulty gene causing Hemophilia-A was given to nine patients. Their blood-clotting proteins went up, they had fewer bleeding episodes and they needed less treatment with clotting factor. A few patients with rarer hemophilia-B have had amazing cures after a single treatment.

The earliest trial by Rosenberg et al, in 1989, used modified tumor-infiltrating lymphocytes to treat melanoma, a then universally fatal form of skin cancer if it has spread to other parts of the body. Other gene therapy treatments have been tried for a fatal primary immunodeficiency disease, and for various inherited muscle diseases, especially in children. Researchers at the University of North Carolina have found a way to change the genetic component of the viral vector carrier, to allow therapeutic genes to get into the brain and cross the previously non-permeable blood-brain-barrier. This barrier is an anatomic structure around the blood vessels in the brain that keeps many chemicals, as well as vital treatments, out of the brain.

By the year 2012, over 1,800 gene therapy trials were completed, ongoing, or approved. Between 1989 and 2015, 2,335 clinical trials related to gene therapy had been completed, were ongoing, or approved (but not started) worldwide. About two-thirds of these gene trials were in the United States. Trials of gene therapy in diseases caused by one abnormal gene were about 10% of the trials, including cystic fibrosis, Huntington's disease, Fanconi anemia, and Gaucher disease. The scientific, humanitarian, and ethical basis for treating these and other diseases with gene therapy relate to the major disability, threat to life, and severe symptoms and problems with

these conditions and the fact there is no present cure or effective treatment available. Two-thirds of the clinical trials were to treat forms of cancer. Many rare diseases cause serious and/or life-threatening conditions. SMA (spinal muscular atrophy) is a rare disease found in infants that affects cells in the spinal cord. It takes away the ability to walk, eat, or breathe. It is the number one genetic cause of death for infants. Most die within the first year of life. Gene therapy has been successful in a few such children.

A comment about the limited clinical trials so far of germline therapy: George Church published a medical article describing compelling reasons for repairing human germ-lines. Whereas a dominant gene, such as SPG4/spastin in HSP, is expected on average to produce the condition in half the offspring and normal in the other half. New adaptations of CRISPR (see my previous CRISPR article in *Synapse*) have been able to increase that proportion from 50% to 72% normal offspring. In the same issue, Brywn Cwik, Ph.D., discusses the design of ethical trials of germline gene editing where the embryo carries a deleterious gene. Recently, researchers have been able to correct a genetic mutation *in human embryos* that leads to a serious heart condition, hypertrophic cardiomyopathy (overgrowth and eventual failure of the heart muscle). There is an ample list of genetic diseases that we would like to see corrected and cured by means of gene therapy. There are still the scientific and ethical concerns about the creation of deleterious off-target mutations. As is common nowadays, the ethical and legal principles and decisions have not kept up with the recent remarkable scientific discoveries and progress. Attorney Mary Schultz will educate us on these complex legal issues related to gene therapy in the next issue of *Synapse*.

What are Gene Carriers/vectors? One important problem is delivery of the new gene to the correct place in the body. A carrier, known as a vector, is genetically engineered to deliver the gene. For example, certain viruses, such as adenovirus and retrovirus, were first used as vectors. Herpes simplex and lentivirus have been used in recent trials, usually modified so they cannot cause disease themselves. In some cases, the virus is also incorporated into a chromosome; in others the virus is simply a delivery vehicle to the nucleus of the cells, the location of the DNA. Sometimes the vector is given into a specific tissue of the body. Sometimes the patient's cells are removed from the body, the vector is attached in the lab and then the "combo" is given to the patient. Concerns with viral vectors are the risk of causing undesirable effects by stimulating the person's immune system, the risk of toxic

side effects, and the problem that the benefit of the viral vector may wear off before the job is done. Other non-viral vectors are chemical and physical systems, including cationic liposomes (fat globules) and polymers, particle bombardment, electroporation (use of electric currents to promote drug absorption into cells), and ultrasound. If successful, the "new" (normal) DNA will instruct RNA to now make the correct protein that was missing or deficient and caused the disease. However, what if the gene therapy makes too much of the desired protein? Would that have undesirable or bad side effects and results?

How does gene therapy work? There is my *Synapse* article describing an amazing new technique called CRISPR, which can correct and/or replace the abnormal gene causing a disease (Winter 2016 issue of *Synapse*, page 16). Gene editing via the CRISPR-Cas9 pathway enabled mice with a gene for hearing loss ("Beethoven mice") to hear better. However, there is the risk of creating new unintended abnormal genes and the possibility of side effects. Much research as well as ethical and cost discussions will need to occur before we can use this method for patients.

Another new tool for gene editing offers new approaches for gene editing to prevent disease. Researchers at Yale have created the triple helix concept, where a gene-editing tool, such as a complex DNA molecule, is carried by nanoparticles (very tiny particles) inside the cell that needs DNA alteration. A normal DNA analog segment, encased in a nanoparticle, enters the cell to form a temporary triple helix, and then the abnormal DNA segment is removed by the body's repair mechanisms, leaving normal DNA, a double-helix, behind. This method of DNA correction has far fewer off-target mutations compared to CRISPR. Researchers have been able to cure a serious blood disease, thalassemia (severe anemia), in a mouse model. This pathway – triple helix - is expected to be in clinical trial within two years.

That's where this new breakthrough, CRISPR, as well as subsequent research advances, such as the "triple helix" gene correction already discussed, may come in and save the day. It's still very early and we need a lot of research to discover just what role these new techniques may have for affected people. A very few persons, children with neuromuscular conditions in particular, have had such treatment with amazing results. Children with spinal muscular atrophy type I, a disease which gradually paralyzes babies, can now be treated with gene therapy that produces a crucial missing protein. Fifteen such treated babies, expected to die by age 2, are alive at 20 months

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or older. Most can sit up and two are walking. We are anxiously awaiting the research progress to include HSP in the group of potentially treatable patients.

Scientific progress in gene editing has been remarkably fast. In March 2018, a Japanese team, Kim, et al, published a new gene editing technique that is now precise enough to modify a single DNA base in the human genome. This is the latest use of CRISPR alongside a DNA repair system. A 45-page highly technical article was published online which, when compared to printed media, greatly sped up distribution of this new knowledge and technique.

The amazing pace of research continues. On March 5, 2018 Stanford researchers, Kramer, et al, published online their research on eliminating the abnormal protein that accumulates in the brains of ALS patients and is believed to be the cause of neuron toxicity. They identified about 200 genes that can either protect the cells from or sensitize them to the toxic proteins. This was done using CRISPR single-guide RNA. Those genes that are protectors of the ALS proteins might be potential drug targets for ALS treatment. As we know, PLS and ALS share some of the same clinical findings and symptoms so ALS research may have a direct bearing on PLS as well.

Ethical Considerations and Issues of Gene Therapy

What are the ethical issues surrounding gene therapy? As stated by the National Institutes of Health (<https://ghr.nlm.nih.gov/primer/therapy/ethics>) they are:

- How can “good” and “bad” uses of gene therapy be distinguished?
- Who decides which traits are normal and which constitute a disability or disorder?
- Will the high costs of gene therapy make it available only to the wealthy?
- Could the widespread use of gene therapy make society less accepting of people who are different?
- Should people be allowed to use gene therapy to enhance basic human traits such as height, intelligence, or athletic ability?

Certainly, the non-availability of Federal funding is a legal issue. Won't wealthy people be more likely to receive gene therapy? That's a serious ethical issue. Gene therapy is very expensive. Would this make it available only to the wealthy? Non-wealthy people need to continue to work, more than wealthy people do, and therefore, what time do they have for lengthy/complex clinical

trials of gene therapy? Are there approved and non-approved gene therapies and locations/clinics where “gene therapy” is performed (like the “odd-ball” non-approved clinics for stem cell treatments)? The ethics of somatic gene cell therapy are complex and the ethics of germline gene therapy are formidable. There is the risk of unwanted mutations elsewhere, unrelated to the disease being treated/prevented, in future generations. The use of germline gene therapy is being considered to likely affect children not yet born who cannot consent to gene therapy that may change their lives by introducing new diseases, etc. Thus, there is no permitted Federal funding for germline gene therapy.

The fundamental basis of mankind, in fact all living beings, is their unique set of chromosomes, mostly the same in a given species, like mankind, but unique in each specific person. Identical twins, of course each carry the exact same set of chromosomes/genes, which is why the first successful bone marrow transplants for leukemia were between identical twins. There would be no immunity and rejection against their own tissue, especially and even if “their own tissue” happens to come from their identical twin!

Our chromosomes contain many thousands of genes that contain the instructions for everything about us. The unique DNA present in each one of us tells our RNA how to make all the specific proteins we need in the correct parts of the body. If there is a defect in our DNA, no protein or the wrong protein is made and a disease may result. Just like “good” and “bad” stem cell treatment centers and treatments, there may be good and bad types of gene therapy. For example, gene therapy treatments might be given without a clear scientific rationale or oversight, by researchers without the necessary training, expertise, and qualifications. One important ethical question is how can we distinguish between the good and the bad uses of gene therapy?

The next ethical question is, who decides which traits are normal and which are a disability or a disease? No one would deny that HSP, PLS, cancer, muscular dystrophy in children, a gene which causes heart failure, blindness, or Huntington's disease, are valid reasons to attempt gene therapy. Suppose the parents are both very short and they wish to have a gene inserted in the embryo of their child to make him taller. Or have blue eyes and blond hair. That's easier to reject, ethically. But there are a whole lot of “middle ground” ethical quandaries. If a serious disease is caused by several abnormal genes, would it make sense ethically to fix only one of the abnormal genes and not know for many years if good results (my grown child will now *not* have an early heart attack), or bad results

might occur (somehow the “new gene” also got inserted into another chromosome, and turned out to cause breast cancer or some other bad result)?

This hypothetical possibility of a new gene affecting future generations is very controversial. While the genetic disorder might disappear, future generations might develop other unknown abnormalities or have long-term side effects. Because those persons who would be affected by germline gene therapy are not yet born, and in future generations not even conceived yet, they cannot make the choice about their ancestors having the gene therapy treatment. These ethical concerns caused the U.S. Government to now not allow federal funding for research on germline gene therapy.

If gene therapy becomes widespread, would these “people who are different” be accepted by society? That seems like a simple question, since you immediately think, “of course!” However, you have all heard about the resistance to selling and eating “genetically-modified food” (GMO) which may have some advantages over natural foods in terms of stability, nutritional value, cost, or longevity. But many people are vigorously opposed to selling and eating foods that are not “natural,” even if, in our opinion, such foods do not present any health hazard or disadvantage to people who eat them. Another ethical question is, should gene therapy be allowed to be used to change or enhance basic



human traits, such as body characteristics - height, obesity that runs in families, IQ, or athletic ability?

With respect to germline gene therapy, even if it were approved and the technical process were perfected, there are specific risks to this type of gene therapy. They include genetic damage to the new person produced by the gene therapy, health risks to the mother while carrying the genetically-altered embryo, and a very low success rate: many embryos and fetuses may be lost. Although germline gene therapy has not been attempted in man, studies in plants and other species have given us important insights. There are two pathways for conducting germline gene therapy. One is to change the genetic content of an extracted egg or sperm, and the other is to change the genetic content of a fertilized egg, done outside the body (called a zygote) and then implant the fertilized egg into the uterus. Recall the contemporary in-vitro fertilization process for infertile couples. Using ‘normal’ eggs and sperm, there may be many successive fertilization attempts to achieve a successful resulting embryo.

Let’s suppose, for the sake of discussion of resulting ethical problems from germline gene therapy, there may be psychological effects. Family relationships may change (“Albert is our smart kid; we made him that way!”), and finally human life may become a commodity. Just like food, there could result two kinds of people: those “regular folks” who are born with their God-given DNA and the other “special folks” whose DNA was altered by researchers, scientists, and doctors who used their God-given skills and abilities to change the DNA, hopefully for the better. Just like that genetically engineered food, compared to regular food.

In somatic cell gene therapy, the injected genes are supposed to be directed by the attached vector to the abnormal/diseased tissue being treated, in the HSP case, the diseased nerves. This does not pass the “new” genes on to later generations, and therefore does not have the same ethical considerations as does germline gene therapy (ignoring the theoretical risk that the eggs or sperm might accidentally pick up the vector/new gene as well as the intended tissues).

Gene Therapy: Summary and Conclusions

Gene therapy is a revolutionary dream come true. It is a splendid and amazing result of the evolution of science after the Watson and Crick discovery, many decades ago, of the structure of DNA followed in recent years by the ability to decipher and define the human genome. We now understand the structure and function of DNA, specifically the genes within DNA. We are beginning to mimic nature and evolution by scientific pathways in addition to the theological and evolutionary pathways which have operated for thousands of years. The few successes in gene therapy so far have helped a few individuals with very rare, usually fatal, diseases for which no other therapy is known. There has been little objection to risking these individuals to the side effects and problems, largely unknown, of gene therapy using our current early and relatively incompletely developed treatment methods and pathways. We are tremendously excited by this revolution in therapy pathways, which over time, research and much discussion, collaboration, and decision-making, is likely to transform medicine in amazing ways. This advance is a medical revolution akin to the discovery of the role of germs in causing disease, the discovery of antibiotics, general anesthesia, vaccination against smallpox and other infections, successful major surgical operations without infections or complications, successful transplantation of major organs (including the heart!)

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and medications that successfully treat major maladies, such as heart, lung, and liver problems. The result of all these advances is the change in life expectancy from 30 or 40 years in the middle ages to 80+ years now. And we hope and believe that to this list will be added the prevention or alleviation of HSP and PLS.

All the answers are not now known or available. Right now, we mostly have two questions. One is how will the remarkable gene therapy research evolve in the next few dozen years to create the ability to replace, alter, or even prevent abnormal genes? The other is how we will be using, medically, ethically, legally, and economically, the amazing new genetic tools to lessen or eliminate the risk and chance of getting a genetic disease, or at least making a genetic disease like HSP or PLS, less troublesome and difficult, or better yet, eliminating such diseases? We can already see a few pots of gold at the end of the rainbow. Come with us and watch what happens when new and brilliant research continues to form new rainbows.

How Can You Help?

Make annual financial contributions to the Spastic Paraplegia Foundation. The SPF's main focus is funding medical research in hopes of finding breakthroughs to find cures for HSP and PLS. The SPF Foundation has already supported researchers who have made major advances in the cause, diagnosis, and treatment of HSP and PLS. Make sure that politicians in your area know that you support medical research, especially rare disease medical research. Be aware of medical research in your area. Offer to participate. Many times, researchers have a hard time finding enough participants to perform their project. There aren't very many of us, with HSP and PLS, so we all need to do our part.

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Germline Gene Transfer <http://www.genome.gov/10004764/germline-gene-transfer/>

Lifecycle of Prescription Drugs

By Jim Sheorn, SPF Tennessee State Ambassador; SPF Board Member

The Food and Drug Administration (FDA) requires all new drugs to undergo clinical trials to insure they are effective and safe enough to use with humans. Each potential new drug first must be identified/discovered in a laboratory setting. Due to strict guidelines and informed consent requirements on experimental testing in humans, these treatments must be first tested in cellular and animal studies before being used in human trials. At this point in the process, an Investigational New Drug application (IND) is submitted to the FDA by the pharmaceutical company. The new drug is then issued a patent by the FDA that is valid for twenty years. Once a potential drug is developed, it can begin the clinical trial process. This process is very expensive and time consuming. The vast majority of potential drugs fail at some point in this process. Pharmaceutical companies and academic researchers usually begin the drug discovery process through research and development projects. Due to the high cost and the high risk of achieving clinical trial success, pharmaceutical companies often license potential drugs to other pharmaceutical companies who then fund the clinical trials.

Clinical testing consists of four successive phases called Phase I, Phase II, Phase III and Phase IV clinical studies.

Phase I Studies – The main focus is to determine the safety and tolerability of the new drug in humans. These studies are generally completed in nine months or less. This is the first time the medication is used with humans. Study participants, usually less than 100, take the study drug to determine how the drug is absorbed, distributed, metabolized and excreted.

Phase II Studies – The main focus in Phase II is to determine the effectiveness and further look at the safety. Depending on the type of drug being studied, this phase takes from six months to about three years. Phase II typically has several hundred participants so researchers can get a consistent amount of data. Minimum and maximum effective doses are also determined in this phase of study.

Phase III Studies – These studies provide expanded testing of effectiveness and safety of a study drug and contain hundreds, if not thousands, of participants. Phase III studies will last from one to four years. Sometimes additional studies are required to help determine safety issues or dosing for specific patients.

Phase IV Studies – These are clinical trials on newly FDA approved treatments to understand side effects over time. These studies may provide additional safety information and help obtain more indications or how the drug can be used. They may even compare effectiveness or cost of a medication already on the market. If the studies are positive, they can help increase revenue for the pharmaceutical company.

Clinical studies can provide the most reliable information if certain criteria are met. They need to be **randomized**. Participants are randomly selected to receive either the study medication or a placebo medication which is typically made of sugar. Participation in a clinical trial does not guarantee the participant will receive the study medication. Some studies may compare the new drug to an existing drug. In those cases, a third group of participants would receive the already-approved competitive drug. Studies need to be **blind**. Participants in blind studies do not know which study medication they receive. In **double-blind** studies, neither the researchers nor the participants know which medication the participants receive. This helps prevent the researchers from treating patient groups differently which could cause the results to be biased in a certain direction.

It is estimated that for every 10,000 new potential medicines identified, just five are considered safe for human trials and only one of those will actually be approved. It typically costs a pharmaceutical company around \$1 billion and takes up to 15 years to bring one new drug to market.

There is a unique challenge posed when developing drugs for rare diseases. Recruiting the number of patients required for traditional clinical trials can be very challenging or even impossible. Specially developed clinical trials that jump from Phase I immediately to a small Phase III trial may be warranted and necessary. Careful planning with the FDA by pharmaceutical companies and patient advocacy groups is very important to ensure maximum benefit to the patient community.

The less time it takes a medication to complete the FDA approval process, the more time there is for the pharmaceutical company to have exclusivity with that drug. For example, if the clinical phases and FDA approval take a total of 12 years to complete, then the new drug can be sold without exact duplication for only 8 years unless the pharmaceutical company receives a patent extension. It's not unusual for a company to modify the original medication making it longer lasting and adding a suffix to the drug's brand name (for example, XR or ER for Extended Release or LA for Long Acting). This

can give the pharmaceutical company an additional three years of patent protection. Once the patent life is complete, generic companies can produce and sell the same exact medication at a reduced price.

The United States is known for high-priced prescription drugs. Some of the reasons are:

Supply and demand – With rare diseases like HSP and PLS, there are smaller populations affected. Pharmaceutical companies will likely charge more per dose since there are few patients available.

Unique mechanism of action – If a drug has a new way to treat a disease and there are no competitors, it allows companies to put a higher price on medication.

Value of medication – The value that a medication brings can be used to determine price. Life-saving drugs will likely cost more. Spinal Muscular Atrophy (SMA) is a rare, progressive disease that affects infants and is life threatening. In 2016, a medication to treat SMA was made available. First year treatment is \$750,000 and then \$375,000 each year thereafter, indefinitely. A more common medication, Viagra, was originally investigated to treat hypertension. It had an unusual side-effect. The manufacturer took advantage of the opportunity and sold it as a medication for erectile dysfunction with a much higher price than if it were just for hypertension. The value had increased. There have been instances of price gouging recently with insulin for diabetes and the EpiPen for those with allergies. Manufacturers have increased prices dramatically because of their value.

As you can see, the life cycle of a prescription medication is complicated, time consuming and very expensive. Hopefully there will be medications made available soon that will help those affected with HSP and PLS. If the studies progress positively with the two drugs currently being evaluated in Australia, the next phase of studies will likely be with humans here in the US. I am ready to sign up. I hope you are, too.

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The Gift Only We Can Give

By Deborah Warden, MD, livingwithPLS@gmail.com

Medical research requires a complex interaction of scientists and support staff, research facilities, resources, and patients.

Patients, families, and friends participate at many levels: raising awareness, raising funds, and participating in clinical trials, among them. Supporting research is the stated purpose of SPF. Donating our brains and spinal cords when we no longer need them is a final opportunity to participate in the search of cures for PLS and HSP.

This article will review the role of autopsy, or post mortem (literally, after death) examination in medical research, possible personal and religious considerations, and practical guidance if you would like to make this precious contribution to medical research.

Direct examination of brain tissue offers information not available from any other test or neuroimaging, making possible the ultimate examination of brain structures, including at the cellular and subcellular levels. Because brain biopsies are not necessary in spastic paraplegia, studying human neural tissue under the microscope is limited to after death.

On our first day of medical school, a lecturer underscored the singular value of the post mortem examination. An autopsy revealed the cause of death for a middle-aged man: hemochromatosis, an illness in which excess blood and iron fill internal organs that gradually stop working. Hemochromatosis is a rare, but not unknown, genetic disease. This discovery permitted relatives to be tested and, if necessary, treated by donating blood often and removing excess iron, thus extending their lives.

One difference is that we know the illness we have, PLS or HSP. Still, post mortem examination can build on recent scientific findings to suggest new avenues of investigation. Also, do we really know that all of us with PLS have the same illness? Many suspect variations of PLS exist and direct examination of brain tissue may help to clarify this, including possibly identifying targets for therapies. Genetics is an integral part of many types of HSP and linking brain and spinal cord findings to specific mutations can only help in understanding the full picture.

Post mortem examinations were done more frequently 50 years ago, both for confirming the reason for death and teaching/research. In "History of the Autopsy" (1973, American Journal of Pathology, pp 514-544), King and Meehan describe how the rise of lab tests, demand for surgical pathology, and opportunities of laboratory research leading to publications were among the factors associated with autopsies being performed less often.

Now, more commonly, specific research groups study brains of patients who had the illness they are studying, often with great insights. One example is traumatic brain injury (TBI) and the Boston VA program studying Chronic Traumatic Encephalopathy primarily in professional football players. These studies have helped redefine the risk we attach to multiple concussions and the sports (and military service) leading to those concussions.

Another example is the Massachusetts General Hospital group that recently published findings of increased inflammation in the brains of people with PLS. (Paganoni S, et al, "Imaging of Glial Activation in People with PLS," Neuroimage: Clinical, 2018, 17: 347-353.) This project built on older publications that included autopsy findings and raises additional questions that new research with post mortem tissue may help answer. The imaging component of this study was funded by SPF.

This group maintains a brain and spinal cord bank for people with Motor Neuron Diseases and has funds to receive donations from people in Massachusetts and nearby areas.

Additional universities have funding for post mortems in motor neuron disease, e.g., University of Pennsylvania. Dr. John Fink at U Michigan has a research interest in the subcellular biochemistry of PLS, which requires careful advanced coordination for donations. Georgetown University also has a brain bank and the Mayo Clinic in Jacksonville, Florida, was recommended as having a neuropathologist especially skilled in ALS/PLS examinations.

However, available funding and personnel can change over time. In 2013, NIH funded the NeuroBioBank (<https://neurobiobank.nih.gov>) initiative to provide a repository for neural tissue. Persons with HSP, PLS, and normal controls are welcome to register. In a brain bank one brain can provide samples to multiple scientists. A single donation form is available at <https://braindonorproject.org> that matches you with a specific center. Forms will be sent to you after registering online. The Brain Donor site includes the story of how it began, inspired by a single patient with Lewy Body Disease who wanted to donate his brain and have it make the greatest impact possible. Six centers are located around the country; each center provides direct contact information on the NeuroBioBank web page if you would rather work directly with one institution. The Harvard program at McClean Hospital is separate from the Massachusetts General group mentioned above. The link to the University of Miami is on the SPF website, <https://sp-foundation.org.presencehost.net>. Preregistration is not required, but greatly preferred. The service is free to donors.

While some religions have not traditionally supported post mortem examinations, the potential for new findings to save lives of others, including children not yet born who may develop genetic illnesses, have prompted reconsideration by some clergy. “To save one life is to save the world” is an important principle in Judaism, though some rabbis require a direct link between the research and saving a life in post mortem donation. Clearly, speaking with your clergy is important.

Not everyone will decide a post mortem is for him/her. We each contribute in our own ways, and brain donation does not have to be your way. However, if you are open to this profound gift you can give after death, here are some practical considerations:

1. Discuss with your family and let them know of your wishes. You may want to confirm that they are comfortable implementing your plan. You may wish to discuss with your clergy.
2. If you are in a research protocol, inquire if that institution does post mortem studies. Communicate ahead of time with the institution where you will be donating.
3. Learn what procedures and requirements are in place at the institution where you will be donating.

Thank you for your interest in this important donation whether you decided to participate personally or not.

4th Annual Meeting of the CReATe Consortium, February 5-6, 2018

By Frank Davis,
President, Spastic Paraplegia Foundation



I attended the CReATe Consortium meeting at Miami Beach. There were about 180 people in attendance,

but only a handful were non-medical people like me. Most of what was talked about was over my head and most was about ALS. However, there were a few discussions that specifically addressed progress with PLS and HSP.

Rebecca Schule, Ph.D. was on the agenda and her topic was biomarkers for HSP. She has just started her biomarker for HSP study so all she could talk about was her planning. She is being sponsored for this study by CReATe and the HSP Research Foundation (Australia). Frank McKeown wrote me in an email that they have supported this study with \$100,000 to determine if NFL (Neurofilament light) is an adequate biomarker for SPG4.

She plans to mainly study NFL as a biomarker which, in past studies, has been shown to be slightly higher for people with HSP than for the control group. It is mainly a biomarker for SPG5. She will find out if it is a good biomarker for other types of HSP.

Stephan Züchner, M.D., Ph.D., said that they discovered a new HSP gene this morning. At first, I thought he was joking, but no, he was serious. They have to validate their discovery but he feels confident they have found a new HSP gene today. *[Editor's Note: Dr. Züchner is a scheduled speaker at this year's Annual Conference in Pittsburgh.]*

CReATe Connect, a Rare Disease Clinical Research Network, reported getting about twice the HSP participation they expected. About 23% of their 700 patients are HSP patients. This is GREAT! More people with HSP and PLS are encouraged to participate! Just go to our SPF website, sp-foundation.org, to find out their contact information all over the United States. I have been participating for a couple of years now. It is relatively easy and just takes a couple of hours every time you attend.

J. Paul Taylor with St Jude's Children's Hospital spoke about a data base they created from the genetic data that has been generated by CReATe. It seemed to be a great computer program that allows scientists to work together in groups or by themselves in a special work space. The program has powerful tools that can be used to work with the incredible amount of data that is created by all the whole genome sequencing that CReATe has done. Their goal is to overcome the barriers that prevents genetic data from curing ALS and related disorders. This program is being released soon.



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There was a long debate on whether or not to release information on VUS (variants of unknown significance) which a lot of people with HSP have. Current policy is to not let people know about VUS as there are concerns about the interpretation. Some scientists said they would want to be notified so they can perform their own studies based on this data.

Of interest, one speaker said that frozen blood samples are kept at -80C. Each of the freezers uses as much electricity as a typical American Household uses in a month. Because of the high cost to maintain frozen samples, they are comparing them to dried blood or plasma. They are heading toward a conclusion that plasma is the best way to go.

Invitae Expands Network of Patients in Rare and Ultra-Rare Diseases

Excerpts from Invitae's March 22, 2018 press release

SAN FRANCISCO, March 22, 2018 /PRNewswire/ -- Invitae Corporation (NYSE: NVT), one of the fastest growing genetic information companies, today announced an expansion of its network of rare and ultra-rare patient registries in its Patient Insights Network™ (PIN) program to include five additional collaborations with leading advocacy groups across a variety of genetic conditions. The programs are designed to empower patients to be active participants in their networks and further expand Invitae's work to connect patients with rare genetic disorders to research, clinical trials and information on managing their condition.

The Spastic Paraplegia Foundation [one of the five additional collaborations] is creating a network for families impacted by Hereditary Spastic Paraplegia or Primary Lateral Sclerosis, a group of rare primary upper motor neuron disorders that cause progressive spasticity (stiffness) and weakness of the leg and hip muscles.

Patient Insights Networks have reimagined the traditional patient registry to maximize the ability of patients to contribute and control their own data and amplify the impact that data can have for other patients, clinicians and researchers. Patient Insights Networks build powerful data sets of symptoms, history, diagnostic journey, quality of life and cost of living with serious health conditions. Patients, advocates, clinicians and researchers then have access to the de-identified data and research-ready patient communities to drive insights that can improve care, increase access to clinical trials and accelerate treatment development. Invitae's program currently covers more than 400 different health conditions. A complete listing of network partners can be found at <https://pindirectory.invitae.com/>.

For more information visit invitae.com/patient-insights-network.

SOURCE Invitae Corporation

An Interview with Craig Blackstone, M.D., Ph.D.

By Allen Bernard

Among a host of CRISPR-related advancements, researchers at NIH are moving closer to drug trials for SPG3A and SPG15.

This a Q&A with Craig Blackstone, M.D., Ph.D., a Senior Investigator at the National Institute of Neurological Disorders and Stroke at the National Institutes of Health in Washington, D.C. Dr. Blackstone is a leading HSP researcher whose laboratory investigates the cellular and molecular mechanisms underlying hereditary movement disorders.

This interview was conducted in March of 2018.



Dr. Craig Blackstone

Dr. Craig Blackstone has been working for years to unravel the mysteries of HSP with the goal of finding a treatment. His lab at the NIH conducts basic research into how HSPs work, the pathology of the disease, so they can begin to test potential therapies.

In just the past few years, Dr. Blackstone and his team have moved beyond understanding the pathology to now identifying small molecules that might work to arrest and, possibly, reverse symptoms in some patients.

What follows is a discussion of the important work Dr. Blackstone is doing in his lab and, more broadly, how HSP research has progressed since our last conversation in the late winter of 2016.

Allen: Hi Craig. Thank you again for making the time for our call.

Craig: Oh, no problem at all.

Allen: Last time we talked you were talking about doing an assay for SPG3A. Has that moved forward?

Craig: We're still working in this area. One thing we've done with our mouse models is we made the symptoms more severe. And the reason we do that is... we want to push the model system. We want to get the mice to have enough of a phenotype that we can see if they respond to therapy. So, we've created a mouse that has a very severe phenotype by mutating several related HSP genes, and now we're trying our first drug trial.

Allen: What is the name of the drug?

Craig: It's a member of the epothilones; there is a whole family of these drugs. We're trying one of them that has good brain penetration when given systemically.

If it looks safe, and if it looks like it's having enough efficacy, then you start to think, 'Well, can we try it in a small human trial to see whether it's safe?'

And, in this case, it will be good because it's been given to people before. And we at least have a started point for how to dose based on previous cancer studies.

Allen: When do you think you will have results?

Craig: Well, in our mice we would know probably within a year to a year and a half. If there's absolutely no concerns, then within a few years, then you could consider a small trial in patients.

Allen: You've always been very confident about the ability of science to find an answer to the HSPs? Do you still believe that?

Craig: Yes, I still do, because there's many examples in other diseases. For instance, cancer treatment is being transformed by advances in immunotherapy, and those advances are based on a molecular understanding of the cancer. In neurologic disorders like spinal muscular atrophy, there have also been dramatic new treatments based on our understanding of disease pathogenesis.

In a sense, what we're doing is not much different. We're trying to understand the very fundamental basis of HSPs so we can have targets to intervene. I think that we've seen enough examples in other disorders where that's worked.

And genetics has been one of the keys. Remember, it's relatively recent that we could obtain this genetic information so quickly. So that's another reason I'm so optimistic. We have new tools that we didn't have before.

Allen: That's great news, Craig. Very exciting. I also wanted to talk about the state of research in general today, if that's okay?

Craig: Sure.

Allen: Specifically, I wanted to start off with gene-editing. I did some basic research by typing "gene-editing" into Google this morning and there is headline after headline about the gene-editing technology CRISPR. It's getting more precise, you know, down to the point where a single letter in a gene can be edited out and replaced successfully.

So, I wanted to get your take on these headlines because, as a lay person, you read these things and you think, "Wow, a treatment is just around the corner." But, as far as actually advancing a treatment, what are these headlines saying to you?

Craig: I think it's incredibly exciting, and as we know more and more about CRISPR and gene editing, it's getting safer all the time. But, like most scientists, the

first thing you think about is, 'What could possibly go wrong? Are there off-target effects? Is it really going to be just as simple when you get into an in-vivo [i.e., in a living being]? Are there going to be any serious adverse effects?' When a technology's new it often hasn't been around long enough to understand possible adverse effects fully.

So that's one issue. But certainly, the idea is very attractive. I mean you go in and fix the basic cause of the disease ... in theory, it should not progress anymore past then, and you might even get improvement from what you had been before.

But it brings up a couple of other points: The first one would be when is the best time to do this? Let's say we could go in and edit a new gene anytime we wanted to. Well, do we have to do it right when somebody's born or could we wait? If so, would they still get the same types of benefits? So, a lot of it is like any therapy: When do you apply it? When can you do it safely? When can you do it and still get maximum effectiveness without having significant risk?

With the nervous system we have another issue, and that's how do you get it delivered to the right cells efficiently. The brain is made of a very large number of neurons that develop in a certain pattern through early life. But let's say we have a 10-year-old and we try to deliver a gene and do this gene repair through CRISPR, how do we know we can get it enough cells to have meaningful improvement?

That's something that we'll eventually learn, but it's also a big issue with neurologic therapeutics in general: How do we get our treatments into the brain? I think many of our therapies can succeed if we can get them to the right cells, and enough of those cells, without adverse effects.

There's also going to be a lot of experience in this relatively soon. So, if there are barriers, people are going to be working on them very hard.

Allen: I see a lot of work in China, other countries. CRISPR is a worldwide phenomenon when it comes to biotech. In China they're using it to treat cancer, build designer dogs. It seems to me that there would be a lot of spill over from this work to address how we can do it in HSP.

Craig: We will get expertise from cancer because in cancer, of course, you can just take different types of cells out of a patient's blood or bone marrow, engineer them, and put them back in; they circulate throughout your body and do their work. And that's why immunotherapy and all these things for cancer have developed so fast.

Continued on next page

Again, our biggest challenge is how do we get our therapies to the cells that are affected in the disease, and in what amounts? If we get it to five percent of cells is that enough? Is 10 percent? Over time, we'll learn the answers to those questions. I think we will get that kind of information relatively quickly.

Our hope is that if we go early enough with the therapy that we'll prevent a lot of the damage, and we'll prevent the disease from really taking hold. But even if you replace a missing protein or fix the genetic defect, is that enough at that time to prevent worsening of the disease or to restore function? We really hope to be able to improve symptoms and stope progression.

Allen: We've talked about this, many times in the past about HSP being an "indicator disease"; a disease that opens the doors to a lot of understanding of other central nervous system disorders, right?

Craig: Yeah, because the upper motor neurons are so long that any other diseases of motor neurons or other types of long neurons may benefit from insights into the HSPs.

Allen: Are you seeing that? We've talked about that now for eight years. Are you seeing proof of that?

Craig: Well, in peripheral neuropathies there are examples. These affect peripheral nerves, but they're also very long nerves. Some of the same genes that cause HSP can give rise to peripheral neuropathies.

In terms of other diseases, I don't know for sure. There are lot of diseases that overlap partly with some of the symptoms that you'd see in HSP. Spinal cord injury and ALS have certain overlapping features.

Allen: What about multiple sclerosis?

Craig: Multiple sclerosis can have symptom overlap, but it's an auto-immune or inflammatory type of disorder. So, it's a different disease even though certainly you can damage the same cells through multiple sclerosis.

There's been some very good developments in terms of therapies for MS. What we learn from MS is that when you do treat people with these medicines you change the disease course and that's a great example for how treatments for neurological disorders are progressing. Certainly, some of the newer developments in spinal muscular atrophy (SMA) are similarly exciting. We know that it's possible for HSPs as well.

Allen: There was a big study that had some very good results here in Columbus [Ohio] at Nationwide Children's Hospital.

Craig: Exactly, amazing recoveries for patients with SMA, and that encourages us all. As we are better able to link different types of HSPs by their clinical manifestations and underlying etiologies, we will have compelling targets for therapies.

Allen: Now, when you say "manifestation", what do you mean?

Craig: Symptoms or other diagnostic findings. If you think about all the different HSPs, you've got this laundry list of disorders. Just as an example, in SPG23 there are pigmentary changes in the skin. SPG25 has, for reasons we don't understand, disc herniations that you'd get in your back.

So, there are some features that are coming up in certain HSPs that we don't 100 percent understand but again it's important to remember these are proteins that often are expressed in a lot of places. In some cases, they may not cause any meaningful problems, so they wouldn't come to medical attention. But you'd say, 'Well, why should we care then?'

Well, one reason is that those can be good biomarkers to follow for therapy because they're easier to access. The brain is so hard to access in terms of following changes in response to therapy, but if there's a change in your blood cholesterol or something easy to measure, then we could easily use that as a biomarker of disease.

Allen: Interesting. So how does that help you move closer to a treatment?

Craig: Well, again, we have 80 genes or so and there are very few diseases that have this many known genes. We're starting to see them coalesce around certain cellular pathways. And some of those pathways are related to other diseases. When we start to see that, that is what moves us closer to therapy. We can begin to target them for drug development.

Usually, at the beginning, we're just trying to correct the cell defect -- like an abnormality in lysosomes. Then, going up the ladder, does it do the same thing to a neuron? Does it do the same thing in a mouse model or a fly model? And, then, does it ultimately work in a person?

So, there's this early pre-clinical development stage, but as you know it gets more and more expensive the farther along you go. So, you want to have good ideas to start with. And, again, the more convergence you have around the pathway of the disease, the more confident you are to devote additional resources.

Allen: Since you bring it up, this seems like a good place to talk about funding. You just got some certainty in this 2018 budget from Congress, right?

Craig: Yes, there's a desire to fund NIH to a very certain level, which is good because, as you know, uncertainty is hard. If you don't know you're going to have money, you might not try to do the experiment.

You don't want to make commitments that you can't meet. So longer-term funding commitments are very important for us. I think there's more certainty now than there has been in the last six months.

Allen: So, with this new funding certainty, are you able to continue to attract top talent?

Craig: In terms of getting people to work in the lab? Absolutely. There is a very large number of young people that want to be physician-scientists and work on disease. We get hundreds and hundreds of applicants each year from people that want to work in the summer or take a year after college. One of the advantages of being in the U.S., at the NIH in particular, is we can draw talent from all over the world.

So, we have no problem drawing really talented people. Another thing about medicine that's changing is it's increasingly drawing different types of people. Before it was mostly biology or chemistry majors, but now you're bringing in computer scientists, physicists, mathematicians -- there's a lot of computational work that's being done. And many of the people in those areas seem quite interested in applying what they know to studies of disease.

So, there's no doubt there's a lot of interest among people that are at the early stages of their career throughout the world. One of the things that people worry about when the funding is more challenging is that we'll lose a generation of these people. You don't want to have them say, "Well, I'm not going to do this." And then go off and do something else. Once they do that, you'll never get them back. So, I think that's another reason for we're encouraged by consistent funding.

Allen: Do you have enough money in your lab right now to do what you want to do?

Craig: I think we have enough, though of course if we had more, we could always do more. But we're quite well-funded certainly compared to other countries and even compared to many laboratories in the United States. The NIH provides us with a lot of resources.

As you may know there's a couple of small HSP-related foundations now that are specifically trying to develop gene therapies. Now, some of that research can be very expensive. And if these foundations can fund these efforts, that can jump-start progress pretty dramatically.

Allen: Okay, good to know. So, overall, where are we along the spectrum of research-to-treatment compared to where we were eight years ago?

Craig: Well, we have identified more genes, right? So, I think the genetic part has been very successful. We have potential targets to guide our studies. And out of that process will come compounds and ideas for drugs. One example is SPG5. They know exactly the enzyme that's involved. They can check its effects in the blood and see the abnormality. And they're already starting to give drugs that can, at least in some systems, reverse the problem. So, you're going to start seeing more and more examples of that where you're moving closer to therapies because now you know what your target is.

Allen: Isn't that about where we were a year ago?

Craig: They are farther along that path. And there's a lot of people starting to try different types of therapies. It was happening a little bit eight years ago, too, but it's happening more now. You're starting to see early phase human trials or certainly therapeutic trials in organisms that are clearly directed more toward the goal of therapy than maybe toward the goal of understanding the disease.

The other big change, of course, is CRISPR and the possibility of gene editing. So, we're starting to see more and more diseases where there is the option to go in and directly change the gene. Of course, that's new. That wasn't something you couldn't do years ago or even couldn't contemplate. That's really been a recent advancement.

At this point in the HSPs, we're starting to get enough ideas of what type of drugs we want to deliver. So, the delivery methods are going to become more important: Do we use viruses? Do we use some kind of nanoparticles that will allow us to get whatever our therapy is to the right place at the right time without a lot of toxicity?

Fortunately, that's the same issue a lot of nervous systems diseases have. So, we could certainly help them but they can help us as well; whether it's Alzheimer's, Parkinson's, whatever, they have the same issue. They're trying to get a therapy into the nervous system without causing a lot of toxicity. So, I think that those fields will advance as well.

Now, it's about working the ideas through the translational system, trying them in cell models and animal models then start getting ideas for what you can try in people.

Allen: This is all very encouraging, Craig. Thanks for taking the time to talk with me today.

Craig: Your welcome, Allen. Any time.

Allen Bernard is a former SPF board member whose daughter was diagnosed with SPG3A in 2006. This article was reviewed for accuracy by Dr. Blackstone.

Connections

Kentucky & Tennessee Connection

March 10, 2018

By Jim Sheorn, SPF Tennessee State Ambassador and SPF Board Member

Twenty people from Tennessee and Kentucky met at Logan's Roadhouse in Franklin, TN, to learn about and discuss several topics related to dealing with HSP, PLS and the SPF. The connection was organized and hosted by Jim Sheorn.

The first topic that was covered was the Biowave, a medical device similar to a TENS unit. It provides electrical stimulation to the skin to help reduce pain. One device will be available in some orthopedic/pain physician offices where you would go in for treatment. There is another unit that can be purchased and used at home. It costs about \$900 for the device and the electrodes that are used are purchased as needed. Some insurance companies cover the cost. If interested, visit Biowave's website, <http://www.biowave.com/#!> and then, if you still have questions, contact me at jimsheorn@gmail.com. Your physician will have to write a prescription in order to obtain.

We talked briefly about a cough medicine called Noscapine. Some overseas folks with HSP are using it as a supplement. I could not find any clinical data about it. If you are on Facebook, go to the Spastic Paraplegia Foundation page and look at a post from Lingarajne Anand on March 8th. It contains information on Noscapine. It is not approved in US. You might be able to order on your own. Please be careful with anything you take as a supplement. It would be best to let your physician know what you are doing to make sure it will not affect anything else you are taking.

Two oncology drugs are involved in research studies in Australia. If either proceeds to further studies, human trials will likely start in the US though it is

not clear when that might be. Feel free to check SPF Facebook and the SPF webpage for updates. Look toward the bottom of the home page for the News & Alerts section. New information is posted there regularly.

An American physician has done some work injecting Mesenchymal stem cells into patients with HSP. This is currently not approved in the US so it is being done out of the country. There is a medical article about scientists using these stem cells on a patient with a crushed back fracture. Please contact me at the above email address if you would like a copy of the article. Hopefully more data will be available soon for those who are interested in this treatment process.

We shared information about some stretching exercises that may be of benefit with those with HSP and PLS. Please check with your physical therapist or doctor before adding any of these to your activities. *[Editor's Note: Please see the article titled, My Home Exercise Program, on page 12 in this issue of Synapse.]*

There is a lot of information and additional resources on the Spastic Paraplegia Foundation, Christopher & Dana Reeve Foundation and the Neurology Now web pages. You can go to christopherreeve.org and Neurologynow.com and sign up to receive free newsletters and other information.

For those that could not attend the connection, please contact me if you have any questions. We will try to have another meeting this Fall if there is interest.



Ahoy Matey, all hands hoay...

ARRRRRR!

YA COMIN' TO
PITTSBURGH

Spastic Paraplegia Foundation
Annual Conference

June 22-23, 2018



Hotel Registration

PITTSBURGH AIRPORT MARRIOTT

777 Aten Rd., Coraopolis, PA 15108, Call 412-490-6604

Free Parking, Complimentary Airport Transportation and Wifi

Hotel Registration: Mention "SPF" for discounted room rate of \$102

Conference Registration

Pay & Complete Registration Online at SP-Foundation.org or

Make Check Payable: **SP-Foundation** Mail Payment/Registration to:

SPF, 1605 Goularte Place, Fremont, CA 94539.

Registration Fees

Adult Early Discount, Must be Paid by April 15, 2018	\$125	QTY: _____	Total \$: _____
Child Early Discount, Must be Paid by April 15, 2018 (under age 18)	\$ 80	QTY: _____	Total \$: _____
Adult Registration April 16th to May 31th, Must be Paid by May 31, 2018 ...	\$175	QTY: _____	Total \$: _____
Child Registration April 16th to May 31th, Must be Paid by May 31, 2018 ...	\$130	QTY: _____	Total \$: _____
Adult Registration June 1st to Onsite.....	\$225	QTY: _____	Total \$: _____
Child Registration June 1st to Onsite	\$180	QTY: _____	Total \$: _____

***To receive discount, payment must be received by SPF.**

Registrant Name#1: _____ Disorder: N/A HSP PLS SP ALS Other

Registrant Name #2: _____ Disorder: N/A HSP PLS SP ALS Other

Child Name #1: _____ Age: _____ Disorder: N/A HSP PLS SP ALS Other

Child Name #2: _____ Age: _____ Disorder: N/A HSP PLS SP ALS Other

Address: _____

Mobile Phone while in PIT: (_____) _____ Text?: Y / N 2ND:Mobile: (_____) _____ Text?: Y / N

E-mail: _____

What aids are you likely to use in PIT? Check all that apply: Cane _____ Crutches _____ Walker _____ Scooter _____ Wheelchair _____

Powerchair _____ Animal _____ Other _____

Meal Requirement: Regular _____ Vegetarian _____ Gluten Free _____ Food Allergies (List) _____ Other _____

Are you driving or flying to PIT? _____

Tentative Agenda

June 22, Friday

1:00pm Welcome

1:30pm - General & Breakout Sessions

5:30pm – Welcome Reception (cash bar)

6:30pm – Dinner, plated

June 23, Saturday

7:30am Breakfast, plated

8:30am – General Session Panel

12:00Noon – Lunch, plated

1:45pm – General Session, Breakout Session

5:00pm Social Mingle (on your own)

6:00pm – Dinner (on your own)

1605 Goularte Place
Fremont, CA 94539-7241



Spastic Paraplegia Foundation invites you to **PITTSBURGH** Annual Conference June 22-23, 2018

\$125 Adult Early Discount, Must be Paid by April 15*
\$ 80 Child Early Discount, Must be Paid by April 15 (under age 18)
\$175 Adult Registration April 16 to May 31, Must be Paid by May 31
\$130 Child Registration April 16 to May 31, Must be Paid by May 31
\$225 Adult Registration June 1 to Onsite
\$180 Child Registration June 1 to Onsite
***To receive discount, payment must be received by SPF.**

Registration Begins January 15, 2018