



BSF breaking boundaries in research, advocacy

In the past, I always felt a little more hopeful in the spring. The promise of new beginnings, the opportunity for growth -- these ideas seemed to be most relevant at a time when the earth was also newly blooming.

This year, however, is different. Over the past 12 months as I have integrated into the Barth syndrome community, I have learned the importance of being both resilient yet compassionate, to stand strong for individuals yet serve as the shared voice of our BSF family, to listen and bend to the needs of our community while also planting strong roots for future partnerships. I have learned that hope is important, but action is critical.

As seasons change, so does the world around us. You'll see in this newly designed newsletter a fresh look for Barth Syndrome Foundation as we share just a few of the incredible endeavors taking place around the globe over the last few months. BSF listened to you and took action. Beginning this year, we will begin to communicate with you more often -- to showcase the work of our researchers -- and

emphasize the strength in our community -- to deepen BSF's relationship with you and hopefully your engagement with BSF.

We intend to be both efficient and cost-effective through electronic newsletters. Please keep in touch with us more often online. In the spirit of spring, BSF encourages you to go green. For those who prefer print communications, we also intend to share our progress with you more often and in a dynamic format.

We are working to modernize our look and method of communicating. However, the mission of BSF and you, our community of families, donors, and scientific contributors, remains tireless and true to saving lives and ending suffering caused by Barth syndrome. Thank you for everything you personally do to help BSF achieve our mission.



From the desk of
Emily Milligan MPH
Executive Director

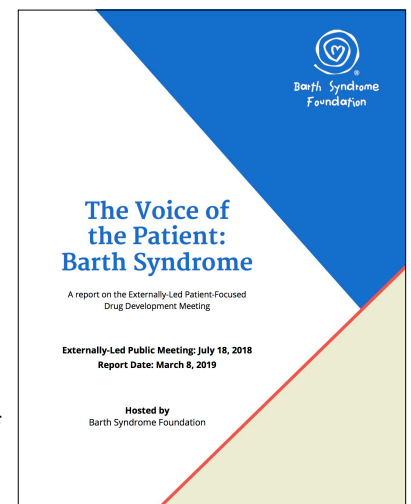
Advocacy in Action

BSF presents Voice of the Patient report to FDA

March 20, 2019, marked another monumental milestone as BSF spent time with representatives from U.S. Food and Drug Administration (FDA) near Washington DC to present the "Voice of the Patient: Barth Syndrome" summary report. Officials conducted a listening session with BSF to learn about the types of therapies that would address the urgent unmet medical needs from Barth syndrome.

Last July, BSF earned the distinction as the 14th organization to ever host an Externally-Led Patient-Focused Drug Development (PFDD) meeting. The event took place during BSF's biennial international conference to share with officials at FDA and other stakeholders from academia and industry the perspectives of people living with Barth syndrome, its impact on their daily lives, and their

Continued on Page 2



expectations and priorities for current and future treatments. The report is a compilation of the testimonies and survey responses of individuals affected by Barth syndrome from all around the world and is the first-ever report of its kind for this ultra-rare condition. According to James Valentine, BSF's regulatory advisor, "BSF brought the voices of all of those individuals from the PFDD meeting to the doorstep of FDA. In doing so, BSF demonstrated the unique value of ways in which patient advocacy organizations can partner with FDA to create an environment that will attract drug development to the space." **Read more at barthsyndrome.org/VOP.**



In back, Tim Maksin. From left, Andrew Buddemeyer, Amanda Maksin, Susan McCormack, Emily Milligan, Kevin Woodward, and Stacey Woodward.



Barth Syndrome
Registry and Repository

BRR 2.0: The power of patient registries

The Power of Patients — Harnessing Quality Registries to Understand Your Rare Disease

Maximizing patient registry data to characterize a rare disease: A decade-long success story from Barth Syndrome Foundation

On Feb. 28, World Rare Disease Day, Barth Syndrome Foundation's executive director, Emily Milligan (right), was honored to represent BSF as an invited participant by the National Institutes of Health (NIH) to discuss the power of patient registries.

Emily joined a group of prestigious panelists from Columbia University, FDA, and NIH and promoted the academic advancements in cardiac function, heart transplants, and neutropenia that have been made possible through BSF's registry.

“Data compiled through BSF’s registry has been the driving factor behind the collective understanding of the disease, as well as a powerful source for directed research strategy and funding.”

- Shelley Bowen

In addition to informing the natural history of disease, BSF has used findings from the registry to inform organizational research priorities.

Shelley Bowen, BSF's Director of Advocacy and Family Services, champions the registry: "Data compiled through BSF's registry has been the driving factor behind the collective understanding of the disease, as well as a powerful source for directed research strategy and funding."

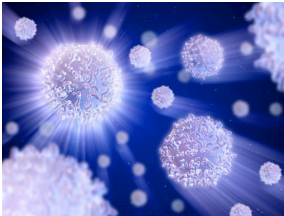


BSF Executive Director Emily Milligan addresses NIH.

In the coming years, and as preclinical work advances to clinical studies, BSF's registry will serve as a critical resource in clinical trial design and execution. Notably, BSF's families and affected individuals are the unsung heroes who have made the findings and future studies possible through their ongoing contributions to the registry. **Read more at barthsyndromeregistry.org.**

Barth Syndrome Registry leads to important clinical findings

Neutropenia, the loss of a certain class of white blood cells, can lead to life-threatening conditions from uncontrolled infection. A recently published study by Colin Steward, "Neutropenia in Barth syndrome: characteristics, risks, and management" from data collected from the Barth Syndrome Registry, highlights the use of granulocyte colony stimulation factor, or G-CSF (Neupogen), to help diminish the dangers from neutropenia. The study, published in the journal



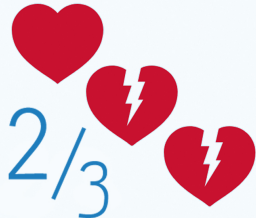
Current Opinions in Hematology (Jan 2019), advocates that a diagnosis of Barth syndrome should be considered in any males with neutropenia who also experience other cardinal symptoms of Barth syndrome. Researchers support the use of Neupogen to help prevent serious infections that are a problem for many individuals with Barth syndrome, especially those who have catheters, PIC lines, pacemakers, or other devices that act as an entry point for bacteria.



Quick facts about Barth syndrome



more than half of all known individuals with **Barth syndrome** experience **fatigue** and **muscle weakness**



reported having **heart failure** or **cardiomyopathy**



70% have **neutropenia**, increasing the risk of infection

12

number of **different doctors** involved in the care of **one individual**



68%

experienced symptoms **before** their **1st birthday**.



>50%

face feeding and **nutrition challenges**



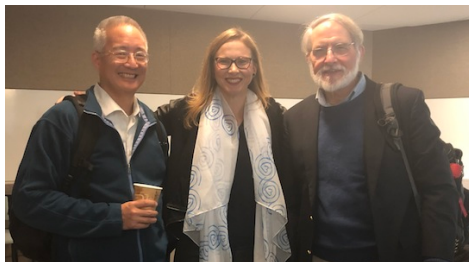
Learn more at www.barthsyndrome.org

BSF Research: From Bench to Bedside

\$400,000 in grants awarded to researchers

For 16 years, the BSF Research Grant Program has strategically funded research projects to improve the scientific and clinical understanding of Barth syndrome, creating a pathway toward potential therapies.

BSF received many competitive submissions in response to our 2018 open call for applications. In spring 2019, BSF funded \$400,000 in new awards across different therapeutic areas being explored by academic researchers around the globe.



SMAB member Dr. Bill Pu (left), Emily Milligan (center), and Dr. Richard Kelley meet in Boston at MitoCase Grand Rounds at Massachusetts General Hospital.

The recent grant cycle continues to showcase a legacy that led to the CARDIOMAN clinical trial in 2019 and more

than 25 awards from NIH to advance research about Barth syndrome. Discovery of viable therapies to alleviate suffering and prolong life for individuals affected by Barth syndrome is the impetus behind our therapeutic research strategy. To that end, the recent grant recipients demonstrated innovative and scientifically rigorous approaches to addressing knowledge gaps in three areas: Gene Therapy; Modification of Cardiolipin; and Improving Mitochondrial Function.

Meet BSF's 2019 Research Grant awardees

RESEARCH FOCUS AREA #1: GENE THERAPY

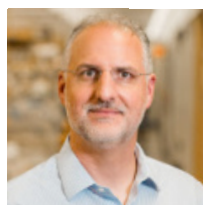
Modifier Gene Research: Dr. William Pu (Boston Children's Hospital)



Pu

Genetic and environmental modifiers are likely to offer insight into the wide spectrum of severity that exists in people with Barth syndrome. **Dr. William Pu** of Boston Children's Hospital will use the genetics of the knockout mouse model of Barth syndrome to identify genes that may modify the high death rate observed in this animal model. Understanding the genetics and the impact of genetic modifiers is important because these genes represent therapeutic opportunities to improve care and treatment of individuals with Barth syndrome. *This grant is made possible by support from the Paula and Woody Varner Fund.*

Appreciating Neutropenia in Barth Syndrome: Dr. William Sykes (Massachusetts General Hospital) and Dr. Christopher Park (NYU School of Medicine)



Sykes

Neutropenia is a serious health risk for individuals with Barth syndrome. However, it is insufficiently understood in its connection to Barth syndrome with the exception that a mutation in the *tafazzin* gene, which causes Barth syndrome, also causes neutropenia in the large majority of individuals. **Dr. David Sykes** of Massachusetts General Hospital will set up a system to allow precursor cells to develop into neutrophils and determine if there are developmental defects that lead to altered immune function. In parallel, **Dr. Christopher Park** of New York University School of Medicine

will investigate whether the neutrophil deficits in Barth syndrome are due to cell-intrinsic defects that occur as neutrophils mature. Understanding exactly how neutropenia develops and appreciating the causal relationship to the *tafazzin* gene should lead to new discoveries of *tafazzin* function that could be therapeutically exploited. *These grants are made possible by support from Association Syndrome de Barth France and Barth Syndrome Foundation of Canada.*



Park

RESEARCH FOCUS AREA #2: MODIFICATION OF CARDIOLIPIN

Lipid Replacement Therapy: Dr. Catherine Clarke (UCLA)

Barth syndrome is associated with a deficiency and alterations in cardiolipin, a phospholipid that is an important component of the inner mitochondrial membrane. This deficiency and alterations in cardiolipin result in damage to the cell. Providing a “disease-resistant” cardiolipin to increase and replace the usual molecules may be therapeutic for individuals with Barth syndrome. **Dr. Catherine Clarke** of UCLA will apply this therapeutic idea by using chemically modified lipids to reduce the amount of cellular damage produced by deficient and altered cardiolipin. If this novel specific lipid-replacement therapy preserves mitochondrial function, it could protect cells against the oxidative stress conditions known to exist in people with Barth syndrome. *This grant is made possible by support from the Will McCurdy Fund for Advancement in Therapies for Barth Syndrome.*



Clarke

RESEARCH FOCUS AREA #3: IMPROVING MITOCHONDRIAL FUNCTION

Mitochondria Restorative Therapy: Dr. Riekelt Houtkooper (Amsterdam Medical Center) and Dr. Jan Dudek (University Medical Center Würzburg)



Houtkooper

Barth syndrome is a unique mitochondrial disease. Another type of mitochondrial disease that has common attributes with Barth syndrome is fatty acid oxidation (FAO) disorders, a group of diseases that affects approximately 1 in 10,000 births, making it 30 times more numerous than Barth syndrome.

Dr. Riekelt Houtkooper of Amsterdam Medical Center will investigate how closely Barth syndrome resembles fatty acid oxidation disorders. **Dr. Jan Dudek** of University Medical Center Würzburg will collaborate with Dr. Houtkooper’s group to study the relationship of fatty acid oxidation and heart failure as it relates to Barth syndrome.



Dudek

These projects aim to explain why underlying defective mechanisms in Barth syndrome impair the body’s ability to use fatty acids properly. Similarly, researchers aim to resolve the cause for the diminished oxidation of fatty acids in Barth syndrome with the ultimate goal of informing novel therapeutic strategies. *Dr. Houtkooper’s grant is made possible by support from Association Syndrome de Barth France. Dr. Dudek’s grant is made possible by support from the Will McCurdy Fund for Advancement in Therapies for Barth Syndrome.*

Cellular Metabolic Improvements Through Nutritional Supplementation: Dr. Miriam Greenberg (Wayne State University)



Greenberg

Metabolic disease disrupts normal metabolism, the process of converting food to energy on a cellular level. At a fundamental level, Barth syndrome is a metabolic disease. For some metabolic diseases, altered nutrition, use of supplements, and/or adhering to a specialized diet may be therapeutic. **Dr. Miriam Greenberg** of Wayne State University will determine why diet supplements may be beneficial to boys living with Barth syndrome by measuring the metabolism of cellular models of Barth syndrome exposed to different amino acids and similar nutrients. The proposed study aims to identify specific metabolic compounds that improve the function of cells that are deficient in cardiolipin. The outcome of this study could provide important guidelines for dietary intervention that may potentially improve the quality of life for Barth syndrome patients. *This grant is made possible by support from the Will McCurdy Fund for Advancement in Therapies for Barth Syndrome.*

Read more at barthsyndrome.org/research.

Therapies within Reach: Clinical Trials

TAZPOWER Open Label Extension

Led by Dr. Hilary Vernon at Johns Hopkins, the Phase 2/3 arm of the TAZPOWER clinical trial ended in December 2018. TAZPOWER was a double-blind, placebo-controlled, randomized crossover trial. The 12 participants received either elamipretide or a placebo for a treatment period of 3 months, then were “crossed over” to the opposite treatment after a washout period. Following completion of the trial in December 2018, participants could elect to stay on the interventional drug during the open-label extension (OLE) period.



Data from the OLE was shared by Stealth BioTherapeutics at the Muscular Dystrophy Association’s 2019 Clinical & Scientific Conference in Orlando, FL, in April 2019. The data suggests that elamipretide may improve functional activity and endurance, quality of life, and reduce fatigue in some individuals with Barth syndrome. Stealth plans to meet with FDA this spring to seek guidance on a potential new drug application. Read more about the first clinical trial completed in Barth syndrome at barthsyndrome.org/TAZPOWER.

CARDIOMAN

The CARDIOMAN trial, the second clinical trial ever to test an interventional therapy in Barth syndrome, enrolled the first patient in the United Kingdom in March 2019! The trial is sponsored by the National Institute for Health Research (NIHR) to test bezafibrate, a lipid-lowering drug that has been safely and broadly used to treat hypercholesterolemia since approval in 1978. CARDIOMAN aims to investigate the effectiveness of bezafibrate on lipid metabolism and subsequent heart function in boys and young men with Barth syndrome. Peak oxygen consumption, as well as heart function of participants during exercise stress, will be measured by cardiac ultrasound imaging.

Notably, CARDIOMAN’s genesis is owed to the long-standing collaboration between Barth Syndrome UK and the University of Bristol to generate critical mass to hit enrollment targets. With incidence estimated at 1 in 300,000, finding eligible patients has been a critical role of the Barth syndrome community to de-risk clinical trial success. Michaela Damin, Barth Syndrome UK’s visionary founder, proposed, “It’s an equation of collaboration. BRHC (Bristol Royal Hospital for Children) brought the academic experts; we found the families. We firmly believe that clinical trials in rare diseases such as Barth syndrome require cross-sector partnership.”

The trial is open to affected individuals, 6 years of age and older. All participants receive 4 months of the intervention (bezafibrate) and 4 months of the placebo, the order of which is determined by computer-generated randomization. Both arms will have a minimum of a 1-month washout period between the intervention and placebo administered, where no treatment is given. Results are anticipated by the end of 2019.

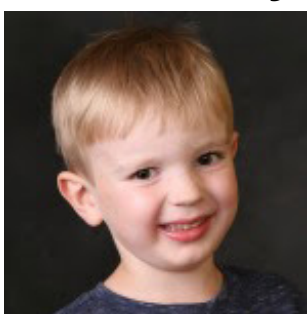
BSF’s Research Collaboration Philosophy:

BSF is steadfast in its commitment to address the critical needs of the Barth syndrome community. We consider all opportunities that propose to accelerate treatments and find a cure for Barth syndrome to end the loss of life and human suffering it causes. BSF recognizes that research and development of new therapies cannot be accomplished without collaboration with like-minded organizations and people in the academic as well as commercial and governmental sectors. BSF does not promote nor endorse any specific therapy, institution, or company. Rather, we are agnostic in our approach and seek to work with any entity willing to partner in the pursuit of our mission and drive the development of scientifically sound, innovative therapies to the benefit of individuals and families affected by Barth syndrome around the world.

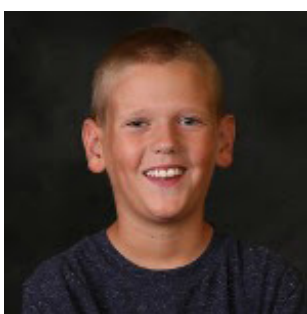
Our community raises awareness on World Rare Disease Day



What do Bryn, Benjamin, and Andrew have in common?

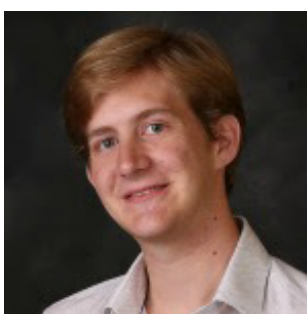


Hope
Community
Magnetic smiles
Barth syndrome



Historically, children with Barth syndrome died of heart failure or infection before 3 years of age, but with improved diagnosis and advances in treatment, their future is brighter.

Help us **#POWERUPBSF** by making a donation in honor of boys and young men like Bryn, Benjamin, and Andrew.



Learn more about our remarkable boys and young men with Barth syndrome, and the work BSF is doing to create a world where Barth syndrome no longer creates suffering or loss of life, by visiting Barthsyndrome.org/ourboys.

"The Foundation is a true example of how groups for rare diseases should be run. The way they bring patients, families, doctors, and scientists together is unique and the amount of knowledge gathered in its mere 18 years of existence is mind-blowing."





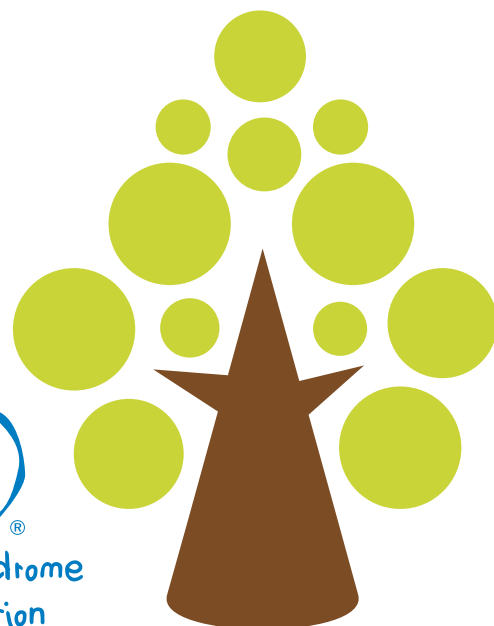
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www.barthsyndrome.org

Go Green for #BarthBlue!

Barth Syndrome Foundation will always be #BarthBlue but we are also going green, and we hope you will, too!

Subscribe to our monthly email newsletter by going to **barthsyndrome.org/gogreen**. You will receive the monthly BSF Research Brief, the Barth Syndrome Heartbeat for Families, Updates from the Executive Director, information about events, conferences and giving, and so much more.

By 2020, we want to reduce the number of mailed pieces coming from BSF. Every printed piece has direct and indirect costs, including printing, postage, sorting, and more. We hope you will go green and join us online.



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