Beyond Batten Disease Foundation: Passion is our driver. Strategy is our compass

Passion is our driver. Strategy is our compass. With your support, Beyond Batten Disease Foundation (BBDF) has developed a dynamic plan to diagnose and prevent juvenile Batten disease while at the same time investing in the most promising research to treat children and families living with the disease. Since the foundation's inception in August 2008, we have made exciting progress. With help from donors, we have 1) developed an easy and inexpensive test to prevent Batten and hundreds of other rare and devastating diseases, and 2) invested in research projects and strategies that are accelerating progress toward a cure.

Our very first goal of creating a test to diagnose and prevent Batten and over 600 other rare devastating conditions is complete, making *Time* magazine's list of Top Ten Medical Discoveries in 2012. Prior to the development of our test, screening for hundreds of rare and devastating diseases was hindered by a lack of availability and the cost of testing for gene defects one-by-one. While most states do screen for 30-50 genetic diseases, this is done as part of newborn screening initiatives, well past the point of prevention. Our multiplex platforms are four times more comprehensive than its nearest commercially available neighbor, absolutely accurate and will cost less than $2 per disease. The test has been beta launched as a diagnostic tool at Kansas Children's Mercy Hospital, where it is helping families avoid the painful diagnostic odyssey experienced by so many of those affected with Batten and other rare diseases.

To reach our second goal of investing in research that will lead to a cure for juvenile Batten disease, we created a strategy for success modeled after and advised by the most successful medical research foundations and government programs, incorporating a business model used by pharmaceutical research and biotechnology companies. This multifaceted approach includes determining what goes wrong on a cellular level to identify drug targets, screening thousands of drugs for their ability to fix cellular mishaps, speeding things up by creating and disseminating new research tools, and preparing for clinical trials. This approach acknowledges that we cannot wait for the next breakthrough to begin recruiting patients and identifying reliable biomarkers for measuring treatment effects. We know that lab-tested treatments are coming. We need to be ready. See a copy of our video for more information: http://beyondbatten.org/videos/research-strategy/

Understanding the progression of the disease on a molecular level is vital to any successful therapy, as researchers must identify the cellular structures and processes that would make appropriate targets for potential drug treatments. Our researchers at the Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital (TCH), the University of Iowa, King's College London in the United Kingdom, the University of Medicine and Dentistry in New Jersey, Weizmann Institute of Science in Israel, and the New York Consortium of Membrane Protein Structure (NYCOMPS) are all exploring the underlying causes of juvenile Batten disease, with an intense focus on lysosomes, the cell's recycling centers that are damaged in patients with the disease.

Drs. Sardiello, Ballabio, and their colleagues joined the Neurological Research Institute of TCH to determine whether activation of master gene *TFEB*, a molecular "switch" that regulates the activity of around 40 genes related to lysosome functioning, induces the production of more lysosomes, to improve the cell's overall ability to degrade accumulated material and inhibit disease progression. The fundamental lysosome problem in juvenile Batten disease is that they work at a reduced capacity and thus get overwhelmed and eventually die, so increasing the number and efficiency of lysosomes in each

cell could compensate for this dysfunction. The beauty of *TFEB* is that it could prompt the cell to fix the problem itself.

Another important project conducted by Drs. Cooper and Williams of King's College London is to investigate whether glial cells, support cells that act as a sort of pit crew for neurons, are malfunctioning and causing damage to neurons. If true, this work will open up a new line of glial drug targets, which may be easier to reach than neurons themselves.

To explore present-day treatment possibilities, we are fueling the Combined Central Nervous System Screening Initiative (CCSI), a simple, cost-effective way to test more drugs in juvenile Batten disease by sharing promising compounds between drug discovery centers and across diseases. Led by the Harvard NeuroDiscovery Center's Laboratory for Drug Discovery in Neurodegeneration at Brigham and Women's Hospital, the CCSI will also serve as a platform for sharing ideas, research tools, and theories about juvenile Batten disease, other neurodegenerative diseases and their common cellular defects. By pooling resources and ideas, the CCSI has the potential to accelerate the evaluation of more than 1 million compounds for their potential to treat juvenile Batten and other neurodegenerative diseases by several years while saving millions spent on current programs. This initiative is representative of BBDF's larger strategy, one that pushes against the traditional model of academic research, which typically encourages self-sufficiency, limits collaboration outside of the academic community, and actually fails to reward translating discoveries into medicines.

The CCSI is one of the steps being taken to combat the sequestration of disease-specific resources among different research groups, which has been shown to hinder progress. An additional effort BBDF is taking is creating and distributing critical research tools that can give researchers a technological "leg up" in their quest for a cure. One of our initiatives is funding the development of hard-to-make CLN3 antibodies, which scientists will use to understand how the elusive juvenile Batten disease protein functions normally and during disease. BBDF also supports the development of animal models that provide important information about lysosome functioning and brain activity incentivizing researchers to place their unique resources in the commercial sector. BBDF successfully applied for inclusion in the National Institutes of Health (NIH)-funded New York Consortium on Membrane Protein Structure (NYCOMPS) to use advanced bioinformatics and structure analysis to better understand CLN3. The information gathered from these efforts will go a long way to informing our drug development and treatment research.

Research is an expensive venture: $1 million is the amount considered by many to be necessary to make a meaningful difference. But according to a June 2011 issue of *Time*, over 90% of 225,000 medical research nonprofits in the US never reach this mark. This is not the case for BBDF. Our very first grant to the Jan and Dan Duncan Neurological Research Institute at TCH in Houston Texas exceeded $2.5 million. Plus, the Will Herndon Fund of BBDF reached its annual $1 million mark in less than 3 years. In just 4 short years, the investments made at TCH have attracted additional funders such as the European Commission, the NIH and the March of Dimes, resulting in $3.7 million in new projects. The ripple effect of BBDF funding is vast: Transcription Factor EB (TFEB), the flagship discovery of [this group], is now being studied in 20 more laboratories around the globe.

BBDF is also outperforming industry standards in the realm of research publications. Over 40% of scientific discoveries never receive attention beyond a single publication, but BBDF researchers publish in the top 1% of 11,000 medical research journals with the highest circulation. The true influence of a publication is often measured in citations, which gives an indication just how important a discovery is by

seeing who mentions the discovery when publishing their own work. BBDF-funded investigators are often-cited and in high-demand.

We are not waiting for accidental victory. Recent developments our understanding of the lysosome, how neurons communicate, and the effects glia may have on neurons along with the increasing availability of previously-unavailable promising compounds to treat disease are resulting in clinical trials for several lysosomal storage diseases like juvenile Batten disease. We believe our turn is next and recognize that a well-designed registry is critical to the success of any trial. Therefore, together with Batten Disease Support and Research Association (BDSRA), Biomarin Pharmaceutical, LLC, Noah's Hope, Blake's Purpose and Our Promise to Nicholas, we are expanding a European Commission-funded, online Batten disease patient registry in Germany, Finland, Italy, India and the United Kingdom into the United States, Brazil, Argentina, Turkey, France, Norway and Denmark. Project teams from each country will work together to collect the world's largest, clinically and genetically best characterized set of Batten disease patients.

For us, there will be only one clear measure of success: providing treatments and a cure for juvenile Batten disease. With your help, we will continue to be groundbreakers. Because of the generosity of our donors and the passion of affected families, we are empowered with funding that drives us in promising directions and provides us with reason to be optimistic, hopeful, and energized to close the gap between here and a cure. Thank you and congratulations on these accomplishments; without your support, they wouldn't have been possible. Please continue to bolster our efforts to find a cure.