

Winter 2012–2013

HELPING HANDS

FOR FRIENDS, FAMILY, AND SUPPORTERS OF THE CHILDREN'S GAUCHER RESEARCH FUND



Summary of Progress

By Greg and Deborah Macres

\$2 MILLION — By Christmas morning 2012 the CGRF will have raised \$2 million since inception in 1999. We give thanks to all of you who have supported this effort – we are humbled by your generosity – and we are more confident than ever that this effort has laid the foundation for significant progress toward a cure.

FDA APPROVAL — In this newsletter Dr. Gregory Grabowski (Cincinnati Children's Hospital Medical Center) will tell you about our initiative to create "A Roadmap to FDA Approval". This initiative, which is being facilitated by the CGRF, is an effort to lay the groundwork for drug therapy approval with the FDA (Food and Drug Administration – USA) and the EMA

(European Medicines Agency). There is no drug therapy yet, but when there is it can take up to two years to prepare the road to FDA and EMA approval. Researchers have encouraged us to build the Road to the FDA now– this tells us they see something on the horizon.

PARKINSON'S — We have talked about the link between Parkinson's and Gaucher disease. Why is this important? There are numerous examples of how research on one disease, sometimes accidentally generates ideas – theories – and then therapies for another disease. In this newsletter Dr. Dimitri Krainc (Harvard Medical School) does a deep dive into this link. It is a bit technical, but he shows that perhaps the two diseases share the same pathogenic mechanism.



Deborah Macres

DEBORAH MACRES R.N.
Founder



Greg Macres

GREGORY MACRES
Chairman/Founder

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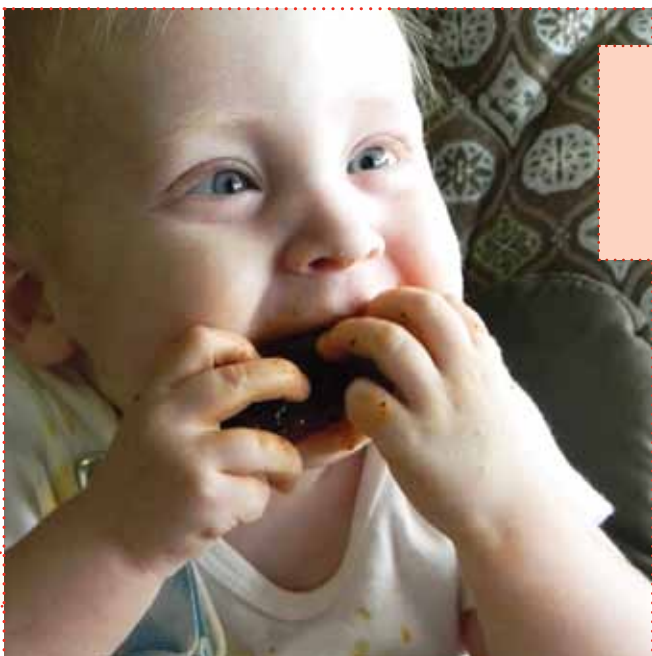
East or west, Dallas is the best

Dallas East Thompson was born during a Texas summer thunderstorm on July 19, 2010. He was welcomed into the world by a family that already loved him very much. There were no immediate signs of what would soon change many lives forever.

At 10 days of age, Dallas' pediatrician detected an enlarged spleen and sent us to the Emergency Room. However, the blood work returned normal so it was decided there was no immediate cause for alarm. With normal family adjustments to a new baby in the home, that first of many ER visits faded into the rear view mirror. His growth and development followed a normal path until 6 months of

age when feeding and weight gain issues were the first sign there was a real problem. Following a lengthy diagnostic process that included a false negative test for Gaucher's, we met with Dr. Raphael Schiffmann in Dallas Texas for a second opinion. He was compassionate, but offered no false hope. Dr. Schiffmann's best advice was for us to take Dallas home and love him, and that's exactly what we did.

Dallas bore all the needle sticks and physical exams with incredible fortitude. He protested of course when being held down for procedures, but did not bear a grudge. Soon he would be playing cheerfully again. His favorite toys were the Learning Farm, xylophone, rattles, and a wooden spoon from the kitchen that he banged on cookware



“Dr. Schiffmann's best advice was for us to take Dallas home and love him, and that's exactly what we did.”

or anything else he could reach with it. In just a little over 22 months he touched the lives of many people. Never without his Binky, Dallas embarked on his most famous accomplishment – adding to his list of girlfriends. Dallas was a lady's man. He flirted with all his female nurses. He had a favorite respiratory therapist and most of all a favorite ICU doctor, Dr. Thapar. Once, she came personally to the ER to escort him to the PICU. The ER doctor said he had never seen such a thing before in his career. Child Life and Pastoral staff were Dallas' fans as well. On his very last stay in the hospital, Dallas was serenaded by a guitar playing Child Life intern and had a concert in his PICU room. After his death, some of the night shift PICU nurses named a star for Dallas that is registered with Name a Star.

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Dallas also loved his home care team and hospice nurse. He got his first toy car from Miss Jenny, a developmental specialist with Texas Early Childhood Intervention program. His home care nurses played with him, read him stories, and made sure that all of his needs were met. Dallas loved to be held. Along with his family, the home nurses spent many hours just holding him. Sometimes, Dallas would not sleep unless he was being held, so that's what we did.

Most of all, Dallas loved his Mom and Dad. Dallas enjoyed hanging out with Dad and watching sports on TV or going outside for adventures in the backyard. Dallas saved his warmest smiles for Mom. As soon as she came into the room, he really did not have time for anyone else.

Dallas got his trach on August 18, 2011 after a respiratory arrest. The day after surgery, Dallas was lying in bed with his right ankle resting on his left knee like he was catching some rays on the beach. A few days later, Dallas sat with help in his Bumby chair so he could bang on his xylophone. Despite sedation making his aim a bit off, Dallas just kept on playing.

Finally, when he could not sit up any more, Dallas played on the floor rolling back and forth while grasping toys or shaking a rattle. When he could no longer do those things, his Nonna would build a stack of blocks, and Dallas would smile as he knocked them down. Then we would do it over again.

On reflection, there is so much more to Dallas' story than the long road to diagnosis and later the unrelenting deterioration of his physical capacity. Actually, Dallas' story is more about love and perseverance in the face of adversity than just a remembrance of tragedy.

Dallas passed away peacefully on June 1, 2012, a bright summer morning. He was in his mother's arms with Dad at his side as always. We miss him every minute of every day. He brought love and joy to his family and caregivers that will never be forgotten.

KAREN AND JUSTIN THOMPSON
Cypress, Texas

A ROADMAP FOR FDA APPROVAL

By Gregory Grabowski M.D.

The advent of effective enzyme therapies for the visceral manifestations of Gaucher disease has stimulated renewed interest in both the basic science and therapeutics for the neuronopathic Gaucher disease variants, types 2 and 3. In May of 2012 a workshop, led by Dr. Tony Futerman and hosted by the CGRF, was held in Atlanta where basic scientists discussed the mechanisms causing the brain disease in Gaucher disease. The discussion was vigorous and will lead to many interesting and important discoveries related to the neurologic involvement in Gaucher disease.

A major recommendation coming from that workshop was to begin the development of a clinical trial protocol for a remaining major unmet medical need in Gaucher disease - treatment of the central nervous system involvement (the brain) in Gaucher disease type 3. The development of clinical trial protocols or assessment tools, that are not specific to the mode of therapy, are critically needed to assess potential therapeutic benefit for Gaucher disease type 3. Because of this general need, the group recommended a new workshop to address the global scope of a treatment protocol or clinical trial design that could determine effectiveness in treating Gaucher disease Type 3 brain involvement.

The workshop members recommended that a small group convene within the coming months to initiate discussions about trial design and to have experts provide measurable outcomes for assessments of new therapies. This would be sponsored by, but completely independent of, at least 4 major companies involved in the treatment of Gaucher disease, including Genzyme/Sanofi, Pfizer/Protalix, Shire/HGT, and Amicus Therapeutics. The workshop would be sponsored and organized by the Children's Gaucher Research Fund (CGRF) and be conducted by independent experts from the United States and Europe. Drs. Gregory Grabowski, from the US, and Ashok Vellodi, from the UK, agreed to spearhead this effort. The workshop will consist of 6 Gaucher experts, 3 from the US and 3 from Europe, with expertise in the neuronopathic manifestation of Gaucher disease. In addition, 1 or 2 additional experts will be involved for specific aspects of neurologic assessments, for example, brain imaging and/or

biomarkers of brain involvement. Each of the companies mentioned above may have one representative at the meeting.

The overall goal of this initial meeting is to develop a common vocabulary and assessments for the neuronopathic involvement by Gaucher disease that will lead to measurable endpoints of clinical relevance to assess therapeutic benefit. These metrics may include overall assessments of cognitive and/or neurologic involvement. The group will also address the issue of reversibility of the brain manifestations. The discussions will be facilitated by a highly experienced physician with extensive previous work with the FDA (Food and Drug Administration – USA) and the EMA (European Medicines Agency) so that a document can be tailored for input from the EMA and FDA. After this initial workshop, a second workshop is anticipated. This second workshop that will include the same group of neurologist, plus representatives of the EMA and FDA, patient groups interested in neuronopathic Gaucher disease, and additional neurologists. Such additional input will be essential. The goal is to produce a document for the overall assessment of therapeutic outcomes of the neurologic involvement in Gaucher disease type 3.

Fortunately, a number of physicians and staff at the EMA and FDA have previous experience in this area and will be able to provide valuable insights and guidance for the final development of a clinical trials protocol. The final product will be a protocol for discussions with the EMA and the FDA in their deliberations of any type of therapy for the neuronopathic manifestations of Gaucher disease. This document will be available in the public domain either as a publication or from the CGRF to investigators and/or companies with a significant interest in developing treatments for the neuronopathic variants of Gaucher disease.



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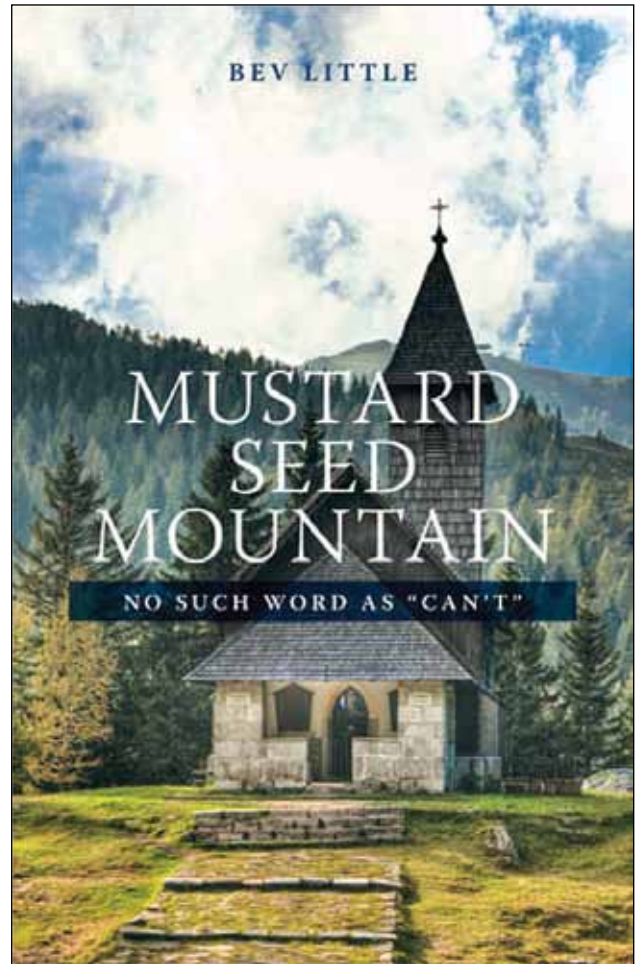
Mustard Seed Mountain

Preface by Deborah Macres



It was late one evening as I was reading some of the notes that often accompany donations to the CGRF. I was captivated by one, a sweet note from Bev Little. She had written a book “Mustard Seed Mountain”, honoring her three

children whose lives were cut short by Gaucher Disease. That night I ordered the book, and by that weekend I could not put this book down. With tears rolling down my cheeks my heart connected immediately with this mother as she told her story of three precious children whose lives were lost to Gaucher Disease in the 1970’s. This is a story of strength, courage and faith, despite some of life’s most difficult obstacles (lack of financial and emotional support - failed marriage - shaken faith – and lack of knowledge about a disease that was killing her babies). In 2011 Bev completed her book honoring her children and dedicated the proceeds to support the Children’s Gaucher Research Fund. I reached out to Bev in a phone call connecting two mother’s hearts as we have both have never given up the fight to find a cure to honor our children’s brave little lives. We both have had two very different lives; despite what resources we each had available, a cure was not in sight for our children. Their courage and our faith have inspired us to continue to fight for a cure for this terrible disease. I encourage each one of you to order and read this book for yourself. It is quick and easy to order on Amazon in paperback and also kindle format.



“IT’S A GOOD LIFE”

Originally published in *The ERA Leader* – Washington Parish - Franklinton, Louisiana.

By Lisa Dykes, Good Living Editor

Dennis was sitting in his recliner watching the ball game. Every few minutes, he’d yell: “Hot dog!” and “Go, go, go!”. It was an exciting game. Me? Well, I was sitting in my recliner next to him, silent, except for the sobbing and sniffing, occasionally taking my glasses off to wipe the tears from my face. I had surprised myself. Crying while reading a book or watching a movie was completely ridiculous, I always thought. But this book was different from any other book I had read. Better than Twilight Saga, taking about 4 hours to read, I just couldn’t put it down. No book has ever gotten my attention like this one.

It’s a story about true love, not a romance novel by any means. It’s a story about a mother’s unconditional love. When tragedy strikes and when facing the unknown, a good mother does whatever it takes to help her children. It’s simple, easy-to-read, written by Mrs. Bev Little about her children and a rare illness, Gaucher, a disease that is mostly found in Louisiana Cajuns and those with French-Canadian ancestry. It is linked to Parkinson’s due to the neurological similarities. Her book is entitled Mustard Seed Mountain.

Mustard seed? Do you know how small a mustard seed is? Jesus tells us about faith that’s the size of a mustard seed can move a mountain (Matthew chapter 17). Mountain? Well, I don’t know if the mountain

represents the disease or the love in Mrs. Bev’s heart. Maybe both.

Mrs. Bev hopes that by telling her story, it will help raise awareness about Gaucher and also encourage others to be screened for the disease. She has spent fifteen years researching Gaucher Type Two and supports the Children’s Gaucher Research Fund.

Mustard Seed Mountain will give you some knowledge about Gaucher. It will inspire you to endure hardships, encourage you to face the unknown, and put love in your heart for humanity. It is available through the publisher, Friesen Press, or Amazon, or Barnes & Nobles. For more information, call Mrs. Bev, visit her website www.intheirnames.com or e-mail her at nevada8774@yahoo.com. Proceeds go to Children’s Gaucher Research Foundation.

Mrs. Bev resides in Washington Parish where she works with OCS and the foster parent program. She is married to Mr. Stanley, who attends Oak Grove Church and always has a hug and smile for everyone.

Well, Dennis finished watching the ball game and went on to bed. Several hours later, after I had finished reading, I joined him in dream land.

It’s a good life!

GAUCHER DISEASE AS A WINDOW TO UNDERSTANDING NEURODEGENERATION ACROSS THE LIFESPAN

By Dimitri Krainc M.D. PhD

The recurrent observation of accumulation and aggregation of mutant proteins in different neurodegenerative disorders indicates the possibility of a shared pathogenic mechanism. Recent data suggest that elimination of mutant protein accumulation can lead not only to a halt of symptomatic progression but also to regression of the disease.

The evidence in Parkinson's disease (PD) is most compelling since the clinical and genetic studies point to a clear dosage relationship between accumulations of alpha-synuclein and disease. For example, subtle alterations in expression level of alpha-synuclein are sufficient to cause a wide spectrum of disease phenotypes.

These findings indicate that if alpha-synuclein can somehow be cleared, the disease can be prevented or even reversed. The clearance of aggregation-prone proteins such as alpha-synuclein is largely achieved through the autophagy-lysosomal system. However, one of the main challenges is to identify specific mechanisms and targets involved in the clearance of these proteins in order to develop specific therapeutics. One strategy to tackle this challenge is to examine rare lysosomal storage disorders (LSDs) that commonly exhibit neurodegeneration and are caused by mutations in genes involved in lysosomal function.

Recent clinical and genetic evidence has identified an interesting link between lysosomal storage disorders and neurodegeneration. The best example of this is the

for GBA1 mutations. Neuropathological analysis revealed the presence of Lewy bodies in the brains of these GD patients similar to those found in idiopathic PD or DLBD. Additionally, genotyping studies using large patient cohorts have identified mutations in the GBA1 gene (that causes Gaucher) as one of the highest risk factor (genetic or environmental) for developing idiopathic PD to date. Therefore, the clinical and genetic link between GD and parkinsonism has been established in "both directions"—patients with GD and their relatives have increased incidence of parkinsonism, and patients with idiopathic parkinsonism have increased incidence of mutations in the gene glucocerebrosidase (GC) that causes GD.

However, the molecular mechanism that would explain how this rare lysosomal storage disorder is linked to adult onset synucleinopathies and neurodegeneration has been largely unknown. In our recent data, we provide evidence that establishes

a link between glucosylceramide metabolism and alpha-synuclein accumulation (Mazzulli et al, Cell, 2011). Using

mouse and human iPS neuronal models, we found that loss-of-function mutations in glucocerebrosidase (GC) result in lysosomal dysfunction, accumulation of alpha-synuclein and neurodegeneration.

An unexpected finding occurred in the course of our studies on the GD-PD linkage: alpha-synuclein was identified as a modulator of GCase trafficking which partially prevents its movement into the lysosome. This suggested that

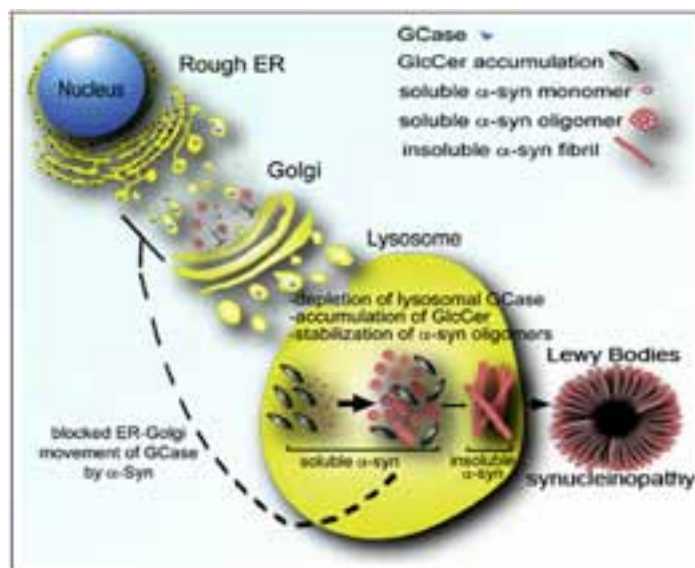


Figure 1: Pathogenic positive feedback mechanism of Gaucher disease and Parkinson disease. Lysosomal GlcCer accumulation accelerates and stabilizes soluble -syn oligomers (bold arrow), which eventually convert into amyloid fibrils (thin arrow). Accumulation of -syn blocks the ER-Golgi trafficking of GCase. Decrease of GCase in the lysosome further amplifies GlcCer accumulation and stabilization of soluble -syn oligomers and results in a stronger inhibition of GCase ER-Golgi trafficking with each pathogenic cycle (Mazzulli et al, Cell, 2011).

accumulation of wt alpha-synuclein alone, an invariable characteristic of all synucleinopathies, can functionally mimic the effect of an established lysosomal enzyme mutation. These results suggested that alpha-synuclein and GC are directly connected in a pathogenic feedback loop leading to a self-propagating disease cycle (Figure 1).

We propose that therapeutic targeting of mutated or normal glucocerebrosidase to lysosomes is expected to prevent or diminish formation of toxic a-syn oligomers and break the vicious cycle of alpha-synuclein aggregation and toxicity. We suggest that this pathway applies to any disease that is characterized by accumulation of a-synuclein including Parkinson's disease. Most importantly, this approach identifies a specific target, glucocerebrosidase, for therapeutic development in Parkinson's Disease and neuronopathic Gaucher's disease.



DIMITRI KRAINIC M.D. PhD
Harvard Medical School

“Most importantly, this approach identifies a specific target, glucocerebrosidase, for therapeutic development in Parkinson's Disease and neuronopathic Gaucher's disease.”

linkage between Gaucher disease (GD) and parkinsonism. It was first noted in 1980 that some patients with GD also exhibit parkinsonism. Several other publications have since confirmed that patients with adult onset GD have up to a 20 fold higher chance of developing parkinsonism or diffuse Lewy body disease (DLBD). More recently in 2004, Sidransky and colleagues noted that patients with GD and parkinsonism frequently had relatives with parkinsonism that were heterozygous



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