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Summer 2014

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


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AN IMPORTANT SCIENTIFIC DISCOVERY

...A Culmination of 13+ Years of CGRF Funding

by Tony Futerman Ph.D. of the Weizmann Institute of Science, Israel


Tony Futerman PhD

It is a couple of years since I last updated you on progress on our research on neuronopathic Gaucher Disease. As some of you may know, the CGRF has been generously supporting work in my research laboratory for the past ten years or so and I am delighted to be able to tell you that this generous support has paved the way for our discovery of a potential new therapeutic target for Types 3 and 2 Gaucher Disease. In fact, the last couple of years have been extraordinarily exciting in my laboratory as we have been able to build on the foundation of the last 10-15 years of research and finally come up with a biochemical mechanism that might explain some of the pathology in neurological forms of Gaucher Disease.

The Story Began...

A couple of years ago when Dr. Einat Vitner, who has been working with me since 2006 and completed her PhD degree a couple of years ago, came into my office one morning to show me what she thought was an interesting result. One of the goals of our work has been to understand why nerve cells die in the brain in Types 2 and 3 Gaucher Disease. Einat had discovered that levels of a certain protein, called RIP Kinase 3 (RIPK3), were significantly elevated in one of the mouse models that we use in the laboratory to study Gaucher Disease. The reason we started looking at RIPK3 was because Einat, along with an MSc student in the lab, Ran Solomon, had found out, from reading the scientific literature, that it was involved in another biochemical pathway which we had earlier shown (with CGRF funding) to be elevated in the brain of Gaucher disease mice; Einat therefore thought it would be interesting to directly test whether levels of RIPK3 were elevated.

A Highly Significant Finding...

At first, neither Einat nor I understood the full significance of the elevation of this protein, but after spending some time learning about the protein itself and the pathway in which it was involved, we began to realize that this finding was highly significant. Over the years, scientists have defined a number of pathways by which

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Inside

CGRF Milestones

■ 1999 CGRF Founded ■ 2001 Funded Basic Science ■ 2009 Funded Mouse Model
■ 2012 Funded FDA/EMA Initiative ■ 2013 Over $2 Million raised ■ 2014 Scientific Breakthrough

Your Support Leads to CGRF Progress

CGRF Strategy: Four Legs of the Stool

Leg 1 = Basic Science
Fund basic science and form the foundation of molecular understanding

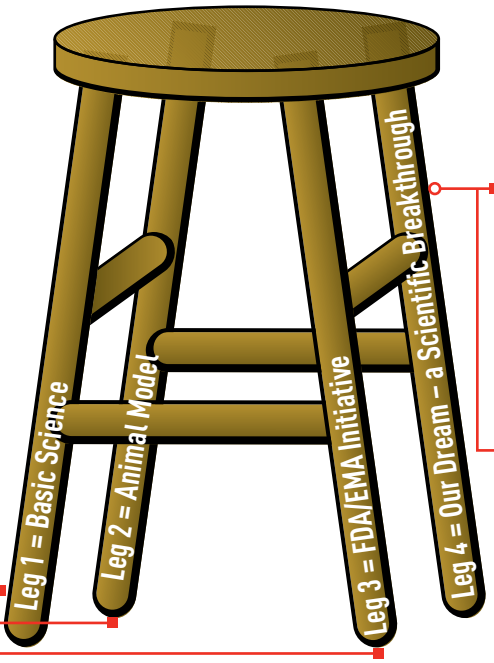
Leg 2 = Animal Model
Create a live mouse model that can be used in nGD research

Leg 3 = FDA/EMA Initiative
Pave the arduous road to FDA/EMA drug therapy approval

Leg 4 = Our Dream – A Scientific Breakthrough
Our goal, and yes our dream, has always been a Scientific Breakthrough

Three Leg Strategy

Knowing that our financial capability is limited, the CGRF strategy has been to leverage our funds to promote research at scientific laboratories around the world. The strategy was to create "Three Legs of the Stool" that will benefit scientists in any laboratory in any part of the world, and compel them to pursue research on neuronopathic Gaucher disease. With your generous support we have accomplished this strategy. Amazingly, your funding of Basic Science has also produced the "4th Leg to the Stool".



Leg 4 = Our Dream- A Scientific Breakthrough

- RIPK3 (see Dr. Futerman's article)
- This Scientific Discovery was funded by your donations to the CGRF
- A direct result of your support
- May lead to the first ever drug for children with neuronopathic Gaucher Disease
- May lead to the first ever drug for children with Krabbe disease
- Could lead to a supplemental therapy for adults with Type 1 Gaucher
- Cautionary Note: With Science, little is certain. Our researchers cannot make promises, however we are extremely encouraged by this discovery. With your help, we will try to transform these results into the first-ever drug therapy for these children.

Parkinson 's disease

- It is already confirmed that there is a link between Gaucher disease and Parkinson's disease.
- This summer (2014) the CGRF is funding the science necessary to determine if this discovery (RIPK3) applies to Parkinson's disease.

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cells die. I won't bore you with the details, but some of these pathways are involved in normal development and some of the pathways are altered in pathological situations in various diseases. RIPK3 was shown, over the past few years to be involved in a very specific pathway of cell death called "necroptosis" and our data suggested that neuronal cell death in Gaucher Disease might occur via this pathway. After educating ourselves about the significance of this pathway, we went on to perform a whole series of experiments and extended our initial observations by showing that the RIPK3 pathway is also involved in a process known as "neuroinflammation" in Gaucher disease.

The Mice Lived Longer... A Lot Longer...

But the most remarkable result was obtained when we examined the lifespan of mice who had been genetically modified so that they did not contain the RIPK3 protein (the use of such mice is very common in modern biology as it allows you to determine whether a specific protein is involved in a specific pathway — we did not generate the RIPK3 mouse ourselves but obtained it from a company who had developed it and published on it extensively). When we induced Gaucher Disease in these RIPK3 "knockout" mice, their Gaucher symptoms improved significantly such that their lifespan was much, much longer than normal Gaucher mice. Not only did their lifespan improve, but a number of other symptoms were significantly

> "...the CGRF has been generously supporting work in my research laboratory for the past ten years... this generous support has paved the way for our discovery of a potential new therapeutic target for Types 3 and 2 Gaucher Disease"

better, including some direct analysis of brain behavior and also some analysis of their liver function, which, I am sure you know, is an organ which is commonly affected in Gaucher disease.

Nature Medicine Publication...

As you can imagine, we were tremendously excited by this data. And fortunately, not only were we excited, but the prestigious medical journal, Nature Medicine, decided that our findings were sufficiently important that they would publish them in their February 2014 issue. Not only did Nature Medicine see fit to publish our data, but a number of journals highlighted our work and we even got

> "... the CGRF had a real understanding and vision that progress in medical science is almost always preceded by progress in basic science ..."

a mention in the Jerusalem Post! Einat was also extremely happy, as she was interviewed on Israeli Radio for about 10 minutes during peak listening hours. So we had our 15 minutes of fame!

Therapeutic Possibilities...

But more seriously, this work is likely to lead to some really exciting therapeutic possibilities. Since the enzymes made by various companies to treat Type 1 Gaucher Disease are completely ineffective in dealing with the brain symptoms of the disease (since they cannot cross the blood-brain barrier), new therapies are desperately needed. One of the reasons that the CGRF has supported our work for so long is that the CGRF had a real understanding and vision that progress in medical science is almost always preceded by progress in basic science; indeed most of our work over the past decade or so has been basic science inasmuch as we have been attempting to understand the biochemical pathway of neuronal cell death, as I mentioned above. Now, from a basic science research finding, we have discovered a novel pathway that should be amenable to pharmacological intervention. This is particularly true since the RIPK3 pathway is apparently involved in a number of other neurological diseases, such as Huntington's Disease, and therefore big pharma is very interested in developing molecules and drugs that will intervene in this pathway. So far, I have had phone conversations and visits to 4

"...we are doing some experiments at the moment (also funded by the CGRF) to attempt to work out whether the RIPK3 pathway might be a link connecting Gaucher and Parkinson's Diseases."

or 5 large companies: the companies are particularly interested in using Gaucher Disease as a model to test their RIPK3 inhibitors since Gaucher Disease, at least Type 1, is well studied.

Parkinson's Connection...

Of course, the connection between Parkinson's Disease and Gaucher Disease has also stimulated the companies to start thinking about therapies that may be effective in both of these diseases and we are doing some experiments at the moment (also funded by the CGRF) to attempt to work out whether the RIPK3 pathway might be a link connecting Gaucher and Parkinson's Diseases. Irrespective of whether this pans out, we genuinely believe that our discovery of this pathway provides some real hope that the development of inhibitors, whenever that might be, will be useful for either directly treating or acting as conjunctive therapy for children with Gaucher Disease.

Although I really don't want to do this, I do need to add a word of caution. I have already received a number of e-mails from the parents of children who have recently been diagnosed with Gaucher Disease type 2 or 3. While my heart goes out to these parents, and while I do my best to understand their hopelessness when told that their child suffers from this awful disease, I must point out that we are still a long way from having a drug that will directly interfere with this pathway and thus be available in the clinic. Development of drugs can sometimes be painfully slow, but because of the great interest in the RIPK3 pathway amongst pharmaceutical companies, I am quietly confident that the day will come when such inhibitors are available both for clinical trials and for use in Type 2 and Type 3 Gaucher Disease patients.

From left to right - Ran Salomon, MSc - Tony Futerman, PhD - Einat Vitner PhD

Cgrf Funding Has Made A Huge Difference...

Let me close by thanking the many generous supporters of the CGRF that have allowed my research to get to this exciting new stage. The CGRF deserves huge credit for supporting a laboratory that is focused on basic research, and I only hope that our work will eventually bear fruition by paving the way for the use of new drugs to treat Type 2 and 3 Gaucher Disease patients.

In Loving Memory of Katie Elizabeth Hancock

Laura Flannery
130 Woodhaven
Mt Lebanon
PA 15228
04-25-14

Greg,

In lieu of gifts on his 8th birthday my son Rowan raised $450 for the Children's Gaucher Research fund. Rowan makes this donation in loving memory of his little sister, Katie Hancock. As a family we continue to spread word of the work that CGRF does.

Please use this money in the development of new drugs or drug delivery systems to treat or cure Gaucher Disease Type 2|3.

Sincerely

Laura Flannery

Laura and Chris Hancock
Mount Lebanon, Pennsylvania

From left to right - Rowan, Aidan, Laura, Katie, Chris

Katie Elizabeth Hancock – May 30, 2012 to February 8, 2013

Katie's 6 month and Aidan's 5 year birthday – from left to right Rowan, Aidan, Chris, Katie, Laura

Courageous Chase

On October 1, 2012, our dream finally came true, Chase Edward Warren was born. Our perfect healthy son or so we thought. We look back on the day we announced Chase's birth and we were specific to note he was healthy after years of trying to conceive and miscarriages. Jay, such a proud father, and I completely in love - there is no other stronger love then the love of a child. The next day during a routine hearing exam, Chase did not pass; we disregarded this to fluid in his ears. Two weeks after discharge we went back for a hearing exam and two more times Chase failed. We thought, "Could it be possible our son is deaf? We did our own tests at home, loud radios, calling him but he was our first child and we were not aware what responses we should get. At one month old during a much more detailed hearing exam we were told he was profoundly deaf due to Auditory Neuropathy Disorder.

"... there is no other stronger love then the love of a child."

As you can imagine this was devastating and our hearts broke learning all the things our perfect son would miss out on. This basically means the ears work fine but there is a loose connection between the ear and the brain, so Cochlear implants were not necessarily an option. We immersed ourselves in the deaf community and preparing life with a deaf child. At 6 weeks old Chase began to scream for hours and refuse to eat. He had severe reflux and we were told he would grow out of it. It was extremely difficult to watch him in pain and not wanting to eat. At 3 months old we began to see that Chase was not growing or meeting milestones. We were referred to every specialist you can think of totaling 13; physical, occupation and speech therapy. We also had a teacher for the deaf come once a week. No one could tell us what was happening to our son.

At 8 months old and several PICU stays and every test you can imagine, Genetics became involved. Chase was 13lbs, could not roll over, his eyes were crossed, he was losing his ability to move, his spine was curved 30%, severe reflux , severe neurological impairment, global developmental delay, severe breathing difficulty, barely able to swallow. We now fed him mostly by syringe to make it easier for him to not have to swallow. We begged the doctors for answers and longed for days when we thought hearing loss was Chase's biggest challenge. He was progressively getting worse but Chase knew life no other way and fought through the choking with a big smile!

"Chase was 13lbs, could not roll over, his eyes were crossed, he was losing his ability to move ...."

He loved to be sung to and read books. If it was up to him he would watch Baby Signing times and read books all day and that's what we did. He loved his dog and family. His face lit up when his daddy came home from work each day. On July 31, 2013 Chase had a spasm in his larynx that caused him to stop breathing and he coded on us. Our neighbor Diane Ruh was able to bring him back but was placed on a ventilator in the PICU. We were waiting on another round of testing from Genetics and we were told on August 1st that Chase had a lysosomal storage disease but they didn't know which one. We were aware of this because of our in-depth research trying to help our son. We knew that because of the degree of his symptoms we didn't have long. We decided to take Chase home with Hospice.

"Two days after Chase passed we received the fatal diagnosis of Gaucher Type 2; there is not a treatment or a cure"

Once home, he rolled over to his left side just as he always did. After a day of singing and cuddles he passed away in his crib surrounded by love and family on August 7, 2013. A piece of our hearts died with Chase that day and we vowed to help others. Two days after Chase passed we received the fatal diagnosis of Gaucher Type 2; there is not a treatment or a cure. These children and parents have no options as with most neurological childhood disease. This is why we are proud to have started ChaseN'Tailz Fishing Tournament in Memory of our beautiful son. We hope to spread awareness about rare diseases and raise funds for them. Most of these diseases are closely related and research for one greatly impacts 16 others. Please help us on our journey to find a treatment.

Summer and Jay Warren
Jupiter, Florida

Pleasant Grove High School KEY CLUB brings together Sacramento area High Schools for their March 2014 Awake-A-Thon ... raising $4,200.00

Lincoln Lewis Wheatley

Thank you Zachary and Kelly Wheatley who each year raise funds for the CGRF. This year the 5th Annual "Play for Gaucher" Charity Poker Event took place on March 29th and raised **$3,600**. Over the past 5 years Zachary and Kelly Wheatley have raised over **$16,000** for medical research.

Robert McCall...To give is to be fulfilled

After losing our son Gregory in 1997 we wrote our families story. In it we wrote:

"Gregory taught us a new way to fulfillment. Prior to his illness we derived fulfillment from receiving; a new car, a hockey game, a vacation. We soon found fulfillment from giving; research, medical care, therapies. He helped us find the strength to rise to the occasion, and we soon found pleasure and fulfillment in the challenge. Our lives will be forever changed. He taught us to give, is to be fulfilled."

What we have learned since is that many other people – our volunteers - in this effort to find a cure find that "to give is to be fulfilled". In last summer's newsletter we thanked Jesus Salcedo who provides our graphic design – free of charge. In this newsletter we would like to thank Robert McCall, who since inception has provided our printing needs – free of charge. In 2013 we decided that printing newsletters for free was enough – and that we should pay Robert for other miscellaneous printing. We thought Robert had agreed and in January we sent Robert a check for $1,500 for stationary and envelopes … two weeks later the check was returned with a note. Robert refused the money … and said he was "in it for the kids". Quite frankly we are speechless – we are appreciative – we feel a bit guilty. It is clear that for Robert "to give is to be fulfilled".

Robert McCall of RPM Printsolutions
rmccall@rpm-printing.com
(408) 813-5307

http://www.childrensgaucher.org/how-to-help/donate-now/

ONLINE DONATIONS

can be made by visiting
www.childrensgaucher.org
OR
www.cgrf.org
All family stories can be read on the web site.

100% TO RESEARCH

You need to know:

1. The CCRF is a *legitimate* IRS approved 501 c3 non-profit organization.
2. *100% of every donation* goes to medical research.
3. We *do not* hire professional fundraising companies who keep 50% of donated funds.
4. We have talented volunteers who *donate* their time and talent for a variety of our needs.
5. All administrative costs are paid for by the *founders.*

Simply put: if you send your hard earned dollars - *It ALL goes to medical research.*

Visit our web site at:
www.childrensgaucher.org
All family stories can be
read on the website.

Contributions Payable To:
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P.O. Box 2123
Granite Bay, California 95746-2123

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