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Summer 2016

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ielping Hands FOR FRIENDS, FAMILY, AND SUPPORTERS OF THE CHILDREN'S GAUCHER RESEARCH FUND Tyler Herre Coope Ashley DeFacci Marsh East Madeline Ansley Thompson Robert Jaynes Watson Valerie losephine Yannias Rose Casares Lampitt Fmma C Dennis lames Danielle Grant & Pozzobon Doran Ir. Conklin Loncharich Garrett Geyer Macres

INSIDE:

Professor Ole Isacson M.D. Ph.D Parkinson's Research Harvard Medical School



Kuldip D. Dave, Ph.D. Director, Research Program The Michael J. Fox Foundation for Parkinson's research



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Roscoe Brady M.D. With Sadness ... With Respect ... With Gratitude



Scientific Conference

Gaucher and Parkinson's: Recent Discoveries and Future Directions





That is a good thing because that is what we are supposed to be doing ... funding science. If you are a long-time reader of this Newsletter you will be amazed (as we are) at the progress. Progress we have made with your incredibly generous support. Comparing this newsletter to those from 10 to 15 years ago ... it is a world of difference.

There was a time ...

... when we were raising funds for research and there was no research to fund. There was a time ... when we were funding basic science on Gaucher disease and it was slow ... plodding ... hard to follow. There was a time ... when many researchers in the scientific community had not heard of Gaucher disease.

Today ...

... there is more research than we have funds to support. Today ... the research we fund will likely help with both Gaucher disease and Parkinson's. Today ... the Michael J. Fox Foundation has a director of research who specifically oversees funding of the GBA research ... the gene that causes Gaucher disease.

Progress is being made, because you have chosen to make a difference.



DEBORAH MACRES AND GREG MACRES



THE ONLY THING INCURABLE IS OUR PASSION

GAUCHER AND PARKINSON'S RECENT DISCOVERIES AND FUTURE DIRECTIONS

Professor Ole Isacson M.D. Ph.D. / Harvard Medical School



Thanks to the compassion and energy of Deborah and Greg Macres, as well as the evolution of my scientific relationships with Tony Futerman (Weizmann Institute, Israel) and Frances Platt (Oxford University, UK), I was fortunate to be invited to this conference (sponsored by the Children's Gaucher Research Fund) on May 6-8, 2016 at Tyson's Corner in Virginia. It turned out to be one of the most interesting and scientifically and medically satisfying meetings I have been to for a very long time. The reason actually is the involvement of the patients and their intense focus of being able to do research that has a meaning and impact on patients' lives, and actually also in this case, potentially the parents and grandparents. The title "Gaucher's and Parkinson's disease" is because when you are a parent or grandparent of a child with Gaucher's disease, you are also carrying a gene-copy that could make it more likely to get Parkinson's disease.

Parkinson's

This was discovered a few years ago by others, and my team, which is specialized on Parkinson's disease, realized that this was an important way to solve both disease problems in a way. The lipid storage effects on cells that create Gaucher's disease may also have the same mechanism that causes Parkinson's disease. It turned out not to be as simple as we first imagined, but one protein that is a problem in cells that die from Parkinson's disease is called alpha-synuclein, and we and others have found that the more that lipids accumulate due to glucocerebrosidase (GBA) loss, the higher the risk that the cells also accumulate toxic forms of alpha-synuclien, causing degeneration of the midbrain dopamine neuron type. These are the cells, that when they die or degenerate -- are responsible for the signs and symptoms of parkinsonism.

In fact, I believe that the work on Gaucher's disease will be an opportunity for Parkinson's disease research and vice versa."

Collaboration

The meeting was very collaborative, and thanks to the efforts of Tony Futerman, who sets the tone of it being a "large lab meeting", everybody was held to collaborative standards that he never wavered on. I am a big fan of this type of meeting where people with very different expertise come together to solve a single or a significant medical problem. This type of science and medical multidiscipline group works when patients are involved, or at least they are the focus of what we do. These

"... I AM EAGER TO CONTINUE TO WORK WITH THE MANY EXPERTS IN THIS FIELD TO MAKE SIGNIFICANT DIFFERENCES IN THE MEDICAL TREATMENTS OF PATIENTS WITH GAUCHER'S DISEASE AND PATIENTS AT RISK FOR PARKINSON'S DISEASE."

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two days of discussions had exactly that format, and I want to congratulate the CGRF on having such a terrific collaborative effort.

What did we learn?

We learned that in fact the so-called lipids (these are fat-like molecules that are normally broken down by enzymes in lysosomes--for example, by GBA. When lipids accumulate inside cells, they can create problems in nerve cells that could create Parkinson's disease. We discussed how that occurs and relates to the fact that Parkinson's disease usually occurs at 60-75 years of age, whereas Gaucher disease occurs in children. The reason appears to be that the very severe elevation of these so-called glycolipids is very traumatic to cells, when we are children; however, having slightly higher levels does not create any problems when we are young, but when the cells age in older brains, they also simulate the same type of problem, but not in the same types of cells as in children.

New Treatments

This discovery is a great opportunity for scientists and medical researchers like myself to figure out new treatments. In fact, I believe that the work on Gaucher's disease will be an opportunity for Parkinson's disease research and vice versa. I work very closely with the Michael J Fox Foundation for Parkinson's Research on their scientific committees and also in their research, and they are dedicating significant funding now for studying GBA. Many scientists who have experience in both fields, including Tony Futerman and Frances Platt, can now influence and apply for funding that gives hope both to patients suffering from Parkinson's disease or the ones at risk, as well as understanding overall the lysosomal storage diseases.

Passion for Discovery

We had many important moments and shared the passion for discovery with the families and patients present. I am certain that the research currently being conducted on Gaucher's disease and now on a broader scale for lysosomal storage diseases, and lysosomal problems in general for neurological diseases, will lead to significant improvements in treatments. Again, I want to congratulate the Children's Gaucher's Research Fund and the dedicated people involved for creating such a fantastic conference, and I am eager to continue to work with the many experts in this field to make significant differences in the medical treatments of patients with Gaucher's disease and patients at risk for Parkinson's disease.

THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH



Kuldip D. Dave, Ph.D. Director, Research Program

I was a bit worried about having this conversation with my wife. It was three days before Mother's day. I had just received an invitation from Greg Macres, president of Children's Gaucher Research Fund (CGRF), to attend their annual meeting in Virginia. But for me to attend this conference, I would need to be away from home on Mother's day. I did finally broach the topic and got approval to attend.

Parkinson's & Gaucher

I am a Ph.D. scientist and work for the Michael J. Fox Foundation in New York. MJFF is the largest non-profit funder of Parkinson's disease (PD) research in the world. Mutations in the GBA1 gene, which produces lysosomal glucocerebrosidase (GCase) protein, have been identified to cause Gaucher disease (GD), a rare lysosomal storage disorder. Mutations in GBA1 also represent the most common genetic risk factor for Parkinson's disease (PD), thus representing a common link between two very different disorders. I am a director of research at MJFF and oversee strategy to advance GBA1 therapeutics. This is why I was so intrigued when I got the invitation from Greg, that I risked asking for my wife's permission to miss Mother's day. It was my opportunity to attend a Gaucher disease conference and see what gaps/challenges exist and what research is being conducted to fill those gaps.

The Link

The link between GBA1 and PD is getting stronger as new research is being explored. The proportion of PD patients that carry GBA1 mutations is estimated to be between 5 and 10%.



"IT WAS MY OPPORTUNITY TO ATTEND A GAUCHER DISEASE CONFERENCE AND SEE WHAT GAPS/ CHALLENGES EXIST AND WHAT RESEARCH IS BEING CONDUCTED TO FILL THOSE GAPS."



The penetrance and lifetime risk of developing PD for GBA1 mutation carriers is estimated up to 20% at 70 years. Reduced GCase activity which is a hallmark for GD has also been shown in PD patients with GBA1 mutations. However, many questions still remain unexplored. We do not yet understand why people with two GBA1 mutations get GD while carriers (that have one mutation) have a higher risk for PD. We also do not know

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why certain GBA1 mutations produce a more rapid progression of the disease or some that produce a slower progression of the disease. While attending the CGRF conference, I realized that those same questions (and many more) are also important and unexplored for Gaucher disease.

World's Leading Researchers

Greg had invited and assembled some of the world's most leading researchers in both GD and PD at this conference. I was impressed by the knowledge represented in that room. The conference agenda was designed to address questions around biology, biomarkers, clinical genetics, and therapeutics. The best part of the conference was that debate and discussion was stimulated and encouraged. I learned that CGRF is funding basic research focused on investigating GBA1 biology in animal models. This research is very important as it allows the field to understand the normal function/role of GBA1 in cells, and also understand how its dysfunction (caused by mutations) can lead to disease pathology. It was sobering to realize that the research challenges and gaps in knowledge for GBA1 and GD are similar to those for GBA1 and PD. It also underscored the need for a complementary strategic roadmap to tackle some of these scientific questions for both GD and PD.

On my way back from the conference on the train, I was thinking that while CGRF's funding is modest compared to MJFF's, the overall mission is similarly big, which is to find a cure for the disease. Oh by the way, I was able to get back into town by 6 pm Sunday. My wife and kids picked me up at the train station and we had a wonderful Mother's day dinner. Thank you Greg and Deborah for the invitation.

WITH SADNESS... WITH RESPECT... WITH GRATITUDE



He (DR. Roscoe Brady) had been nominated several times for the Nobel Prize in Medicine by other Nobel Laureates. January, 1994, we arrived at the National Institutes of Health (Bethesda, Maryland) with our 1-year-old son Gregory who had just been diagnosed with Gaucher disease. Young ... new parents to our second child ... anxious ... frightened ... still trying to pronounce "Go-Shay" ... and praying for some glimmer of hope ... praying that someone had devoted their career to the study of Gaucher disease. We found that person ... it was Dr. Roscoe Brady.

As soon as we arrived there was talk of Dr. Brady. He had been nominated several times for the Nobel Prize in Medicine by other Nobel Laureates. Staff at the NIH talked of how he had devoted his life to lysosomal storage disorders – how against all odds he fought the nay-sayers – for years he confronted and overcame obstacles – he finally discovered enzyme replacement therapy that improved the lives of thousands of patients around the world.

It was Day 3 of our visit when Dr. Brady would accompany the "Medical Rounds" – the day we would finally meet him – and the day he would assess Gregory. We had done our research and knew that he had joined NINDS (National Institute of Neurological Disorders & Stroke) in 1954. We are pretty good at math so that put him at NINDS for the past 40

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years. A logical concern ... "Is he going to retire soon"?

Dr. Brady did not retire until 2006 ... serving over 50 years at the NIH ... and ...He continued to serve as a Scientist Emeritus coming to work every day until just weeks before his passing.

For more than 50 years Dr. Brady studied these hereditary disorders, identifying the causes of Gaucher's, Neimann-Pick, Fabry, and Tay-Sachs diseases. He and his colleagues developed diagnostic tests and spearheaded the development of enzyme replacement therapy for these and other lysosomal storage diseases, which led to the first effective treatment for many rare disorders. Along the way he published hundreds of research articles, trained many doctors, received several well-deserved awards and until very recently he regularly attended and contributed to the discussions at NINDS grand rounds and scientific conferences.

With Sadness ... With Respect ... With Gratitude. Those who knew him best remember his kind and mentoring nature, how deeply he cared about the NIH and the research he conducted over many decades, and his devotion to improving the lives of the patients he served.

JOHN BARRANGER MEMORIAL RESEARCH GRANT



In Grateful Memory of John A. Barranger, M.D., Ph.D., Sanofi Genzyme Corporation has established the "John Barranger Memorial Research Grant" that will annually fund \$75,000 of medical research on neuronopathic Gaucher disease. Sanofi Genzyme has entrusted this grant to the Children's Gaucher Research Fund, giving us the honor of managing the call for research, the meticulous review of research proposals, the funding of research, and the follow-up to ensure research progress. Sanofi Genzyme has honored a man who dedicated his life to helping patients with Gaucher disease, and what better way than to support the funding of medical research.

A champion for those with lysosomal storage disorders Dr. Barranger was a man who devoted himself to research and to patient care; always an advocate for those who suffer from Lysosomal storage disorders. Dr. Barranger also served on the Scientific Advisory Board for the Children's Gaucher Research Fund. On



"IN 2016, PROFESSOR RICARDO A. FELDMAN OF THE UNIVERSITY OF MARYLAND WAS AWARDED THE "JOHN BARRANGER MEMORIAL RESEARCH GRANT".

May 25, 2014, the Gaucher community and the Lysosomal disease community at large lost a friend, an advocate, and a great mind.

"In 2016, Professor Ricardo A. Feldman of the University of Maryland was awarded the "John Barranger Memorial Research Grant". We thank Sanofi Genzyme for their selfless gesture to honor a good man, and to give hope to families affected by Gaucher disease.

SANOFI GENZYME 🎝

We thank Sanofi Genzyme for their selfless gesture to honor a good man, and to give hope to families affected by Gaucher disease.

SCIENTIFIC CONFERENCE GAUCHER AND PARKINSON'S Recent Discoveries and Future Directions May 2016

"IT WAS A REAL PLEASURE TO MEET ALL OF YOU. THANKS SO MUCH FOR GIVING ME THE OPPORTUNITY TO BE PART OF THIS UNIQUE GATHERING. I THINK OUR THEME NEEDS TO BE UNIQUE TOO ... "TOGETHER WE CAN MAKE A DIFFERENCE TO THE GD/PD COMMUNITY". THANKS GREG AND DEBORAH FOR ALL YOUR EFFORTS AND DEVOTION. THANKS TONY AND RAFFI FOR ARRANGING THE SCIENTIFIC PART. LOOKING FORWARD TO OTHER SIMILAR MEETINGS."

> Magy Abdelwahab, M.D, Ph.D. Cairo University Pediatric Hospital Cairo. Equpt

"THANK YOU FOR ORGANIZING SUCH AN EXCITING MEETING, AND FOR BRINGING TOGETHER SCIENTISTS WITH FAMILIES THAT HAVE SUFFERED THE LOSS OF THEIR PRECIOUS ONES. AS THE TRANSLATIONAL SCIENCE IS MOVING FAST, I HOPE WE ARE CLOSER TO THE DAY WHEN THIS DREADED DISEASE SHALL BE OVERCOME. WE WILL DO EVERYTHING WE CAN TO MAKE THIS HAPPEN."

Ricardo A. Feldman, Ph.D. University of Maryland School of Medicine Baltimore, Maryland, USA "IT WAS A PLEASURE TO MEET YOU AND OTHERS AT THE GD/PD MEETING! MEETING FAMILIES AFFECTED BY GD PUT A REAL FACE TO THE SCIENTIFIC PROBLEMS WE ARE WORKING ON. I WALKED AWAY FROM THIS MEETING WITH A RENEWED SENSE OF PURPOSE OF MY WORK! ALTHOUGH I AM AN OUTSIDER IN THE GD FIELD, I WILL BE DELIGHTED TO CONTRIBUTE WHAT I CAN (MOSTLY AS TONY'S COLLABORATOR)!"

Francis Chan, Ph.D. University of Massachusetts Medical School Worcester, Massachusetts, USA

"I WANTED TO PERSONALLY THANK YOU FOR HAVING ME IN THE CONFERENCE. IT'S A GREAT PRIVILEGE TO WORK AS PART OF THE SCIENTIFIC COMMUNITY YOU AND THE CGRF HAVE CREATED. WHAT WAS REALLY UNIQUE ABOUT THIS CONFERENCE IS SEEING PEOPLE FROM SUCH DIVERSE DISCIPLINES ALL PUTTING THEIR HEADS TOGETHER TO TRY AND MAKE PROGRESS IN UNDERSTANDING GAUCHER DISEASE AND TAKE ANOTHER STEP TOWARDS FINDING A CURE. PHYSICIANS, CELL BIOLOGISTS, GENETICISTS; PROFESSIONALS FROM THE PHARMACEUTICAL INDUSTRY WORKING ALONGSIDE RESEARCHERS FROM THE ACADEMY AND HEALTHCARE PROFESSIONALS TOWARDS A COMMON GOAL. MEETING WITH THE FAMILIES AFFLICTED WITH THIS HORRIBLE DISEASE PROVIDED A HEART-RENDING TESTIMONY TO THE URGENCY AND IMPORTANCE OF THESE EFFORTS."

> Einat Vitner Ph.D. Institute for Biological Research Ness Ziona. Israel

"FIRST OF ALL, THANKS TO TONY FOR ORGANIZING A STIMULATING AND EXCITING CONFERENCE, AND TO THE CHILDREN'S GAUCHER RESEARCH FUND FOR THEIR SUPPORT AND INSPIRATION! I AM WRITING TO FOLLOW-UP ON OUR DISCUSSION ABOUT BUILDING A RESEARCH CONSORTIUM. I AM INVESTIGATING POTENTIAL FUNDING FROM THE NIH AND WILL COMMUNICATE FURTHER WHEN I HEAR BACK. THESE ARE EXCITING TIMES, WITH NEW TOOLS AND RESOURCES! THERE IS NO DOUBT THAT OUR COMMUNITY, WORKING TOGETHER AND COMBINING SAMPLES, WILL MAKE A MARK BOTH IN UNDERSTANDING PHENOTYPIC HETEROGENEITY IN A SINGLE GENE DISORDER, AND IN IDENTIFYING GENES AND TARGETS RELEVANT TO PARKINSONISM."

> Dr. Ellen Sidransky M.D. Chief, Section on Molecular Neurogenetics MGB, National Institutes of Health Bethesda, Maryland, USA

"I THANK THE ORGANIZERS AND ALL PARTICIPANTS FOR THE GREAT CGRF 2016 MEETING. THIS MEETING WAS UNUSUAL IN THE SENSE THAT IT BROUGHT TOGETHER WORLD EXPERTS IN MANY FIELDS: CLINICAL GAUCHER'S DISEASE, CELL BIOLOGY, BIOCHEMISTRY AND GENETICS. ALL PRESENTATIONS AND DISCUSSIONS WERE DONE IN A COLLABORATIVE AND COLLEGIAL MODE. IT ALSO HIGHLIGHTED THE IMPORTANT CONNECTION BETWEEN GAUCHER'S DISEASE (GD) AND PARKINSON'S DISEASE (PD), AND OPENED THE VENUE FOR FURTHER ADVANCEMENTS IN THESE FIELDS, FOR THE BENEFIT OF GD AND PD PATIENTS AND FAMILIES."

> Prof. Avi Orr-Urtreger, M.D., Ph.D. Director, Genetic Institute Tel Aviv Sourasky Medical Center Tel Aviv, Israel

Gaucher Research Fund

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

ONLINE DONATIONS

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.

- Contributions Payable To: Children's Gaucher Research Fund P.O. Box 2123 Granite Bay, California 95746-2123
- Visit our web site at: www.childrensgaucher.org All family stories can be read on the website.