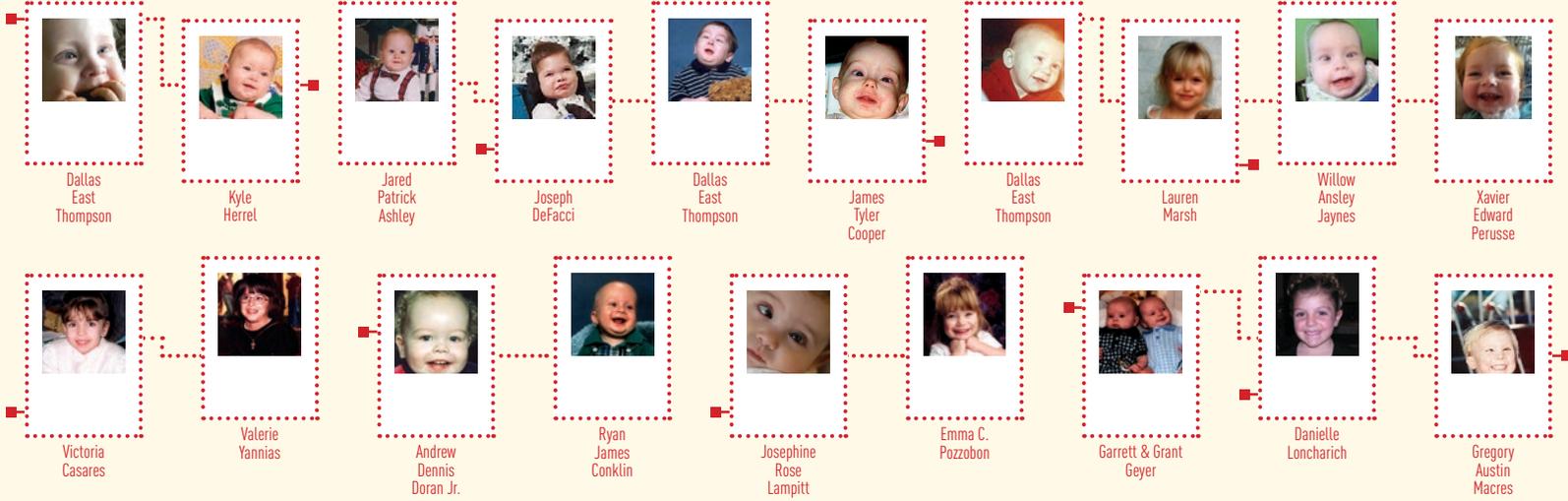


SUMMER 2017

HELPING HANDS

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



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INSIDE:

Sanofi Genzyme Funds Year 2 of Research

Honoring Dr. John Barranger Sanofi Genzyme funds a second year of the "John Barranger Memorial Research Grant".

SANOFI GENZYME 

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WHERE YOUR DONATIONS ARE SPENT

Medical Research 100%

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100% to Research

Our long-time donors know ... 100% of every donation received by the CGRF goes to fund Medical Research. There are no salaries, and all administrative expenses are paid for by the founders, Greg and Deborah Macres. This is important to us, that you know our only motivation is to give hope to families, and give life to those children afflicted with Gaucher disease.

Futerman at the Weizmann Institute of Science began in 2001, and continues today. Our most recent funding (beginning in 2016) of research has been with Dr. Feldman at the University of Maryland. In this issue, Dr. Feldman shares with you progress in the first year of CGRF funding.

Join Us

This issue is packed with science. Our intention is not that we all become experts in the science. Our intent is to show you that progress is being made. Clearly, the path is long, and the path is difficult. But together, with unrelenting resolve we seek to do the impossible. We ask that you "Join Us".

Are We Making Progress?

Rather than tell you ourselves, we thought we would let experts in the field tell you by printing "A Message to CGRF Donors" from three prominent experts in Gaucher Disease. What they want to say to you ... is printed on the following pages.

\$300,000 Annual Funding

For the third year in a row the CGRF is funding \$300,000 of medical research. Funding for Dr.



DEBORAH MACRES AND GREG MACRES

A MESSAGE TO CGRF DONORS FROM PROFESSOR TIMOTHY M. COX



Professor Timothy M Cox
Professor of Medicine Emeritus,
Director of Research,
Life Fellow of Sidney Sussex College,
University of Cambridge UK

It is timely to celebrate the extraordinary support provided by the CGRF for state-of-the-art research into the nature of the neurological inflammation and injury that occurs in brains of babies and very young children who suffer from the most severe forms of Gaucher disease. The laboratories of Dr Tony Futerman from the prestigious Weizmann Institute of Science in Israel and Dr Ricardo Feldman from the

University of Maryland Medical School are recent recipients of generous and discovery enabling CGRF grants.

So far, unlike other forms of Gaucher disease, there is no effective treatment or immediate promise of relief for type 2, the acute neurological variant. The 'market' would be tiny and the means to do this not at all clear. Readers know of the relentless assault on the brains of babies and the very young – and the cruel fate of those families affected. At the same time, while the disease is rare, expertise is even rarer – so that devastated parents and families have nowhere to turn for support. Very few scientists and researchers are brave enough to get involved in such a neglected and demanding field.

Prof Futerman's courageous partnering with the Macres family and the Donors of CGRF, has led the way for many years: a circle of international collaborators has built a game-changing portfolio of research directions which, in wholly novel ways, address the lethal features of inflammation that lead to the misery of brain injury. High-level publications document these outcomes and have already opened up avenues for promising intervention and therapy.

There is symmetry with the newly supported programme of research by Dr Feldman: this has

the potential to move hand-in-hand with Tony Futerman's: neurons cultured from patients harbouring mutations responsible for Gaucher disease are now becoming available for the first time. The Feldman laboratory has used the latest reprogramming technology to generate these precious neurons from skin fibroblasts obtained almost noninvasively from patients. In a process akin to biological alchemy, key reprogramming factors are introduced and all types of Gaucher disease can be studied. The method yields induced pluripotent stem cells (iPSCs) which have invaluable properties for modelling the disease and exploring therapies. The iPSC-derived cells recapitulate cellular abnormalities seen in patients, and are also facilitating drug discovery: the group have already been able to reverse the loss of dopaminergic neurons in their 'disease-in-a-dish' model of the developing brain and several new drug leads are actively being explored.

The potential synergy between these groups supported by CGRF is extraordinary: beyond counselling and practical support, the charity has led the way to bring about radical changes in confidence and preexisting concepts. For this rare variant of Gaucher disease, the charity has had an instructive influence already but ahead lie plans for more intensive community engagement and experimental trials. The Fund was founded by dedicated people who turned the pain of their own loss into a special type of public good. I can only celebrate their strong interactive spirit and the energy stimulated by CGRF; finally, we congratulate all on this productive tranche of new clinical science. ■

A MESSAGE TO CGRF DONORS FROM FRANCES PLATT, PH.D.



Frances Platt, Ph.D.
Professor of Biochemistry
and Pharmacology
Dept. of Pharmacology
University of Oxford
United Kingdom

The work of Dr Futerman is providing important insights into the underlying disease mechanisms leading to neuronopathic Gaucher which in turn is suggesting new avenues for therapy. Another very exciting addition to CGRF funded research is the work of Dr Ricardo Feldman

who is using innovative stem cell approaches to better understand at the cellular level the link between GD and PD. The two research projects are complementary and advancing our knowledge which will ultimately lead to new treatments. ■

A MESSAGE TO CGRF DONORS FROM PABLO SARDI, PHARM.D., PH.D.



S. Pablo Sardi, PharmD, PhD
R&D Director
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Sanofi Genzyme, Corp.
Cambridge, Massachusetts

In the last decades, we have seen an unprecedented advance in the understanding and treatment of Gaucher disease. Still, there are many critical unmet medical needs. The research funded by CGRF provides high value to the scientific and medical community. It is critically important to understand the mechanistic basis

of diseases and to explore the out-of-the-box ideas that might lead to novel treatments. These discoveries require multidisciplinary teams aligned towards a common goal. CGRF funding acts as a key catalyst for these international collaborations. ■

GLOSSARY

Dopamine

Dopamine is a neurotransmitter, one of those chemicals that is responsible for transmitting signals in between the nerve cells (neurons) of the brain. Very few neurons make dopamine. Some, in a part of the brain called the substantia nigra, are the cells that die during Parkinsons disease.

ERT

Enzyme Replacement Therapy ... Intravenous infusion into patients of a pharmaceutical preparation of the missing enzyme; the infused enzyme cannot cross the blood-brain-barrier.

Fibroblasts

Skin cells

GBA1 gene deficiency

GBA1 is a gene in the body that when mutated does not work correctly - it does not make an important enzyme (Glucocerebrosidase). GBA1 is also referred to as "the Gaucher gene".

Glucocerebrosidase

An enzyme that is needed for good health and is encoded by the GBA1 gene. This enzyme prevents the abnormal accumulation in the body of a lipid substance called Glucosylceramide.

Glucosylceramide

A lipid in cells that is digested (broken down) by the enzyme Glucocerebrosidase". When the body produces insufficient enzyme, Glucosylceramide accumulates in the body.

Induced Pluripotent Stem Cells

Also referred to as iPSC cells, are cells taken from a tissue (usually skin or blood) from a child or adult and are genetically modified to behave like embryonic stem cells. As the name implies, these cells are pluripotent, which means that they have the ability to form all cell types.

Lysosome

Inside a cell, numerous organelles function to remove wastes. One of the key organelles involved in digestion and waste removal is the lysosome. Lysosomes are organelles that contain digestive enzymes. They digest excess or worn out organelles and engulfed viruses or bacteria.

Macrophages

The macrophage is a large white blood cell that is an integral part of our immune system. Its job is to locate microscopic foreign bodies and 'eat' them. Macrophages use the process of phagocytosis to engulf particles and then digest them.

Microglia

Microglia are a type of neuroglia (glial cell) located throughout the brain and spinal cord. Microglia account for 10-15% of all cells found within the brain. As the resident macrophage cells, they act as the first and main form of active immune defense in the central nervous system (CNS).

Mutation

A gene mutation is a permanent alteration in the DNA sequence that makes up a gene, such that the sequence differs from what is found in most people.

nGD

Neuronopathic Gaucher Disease - the type of Gaucher disease that affects the brain.

MECHANISMS BY WHICH GBA1 DEFICIENCY CAUSES NEUROLOGICAL DAMAGE



Ricardo A. Feldman, PhD.
Associate Professor
Department of Microbiology and Immunology
University of Maryland School of Medicine
Baltimore, Maryland

ERT has brought relief to many patients affected by type 1 GD, the non-neurological form of the disease, but because the therapeutic enzyme cannot cross the blood-brain-barrier, ERT cannot be used to prevent the neurological damage in nGD, which is irreversible. A few laboratories are working intensely to find new treatments for nGD.

Our Laboratory's Focus

Our laboratory is focused on understanding the mechanisms by which GBA1 deficiency causes neurological damage (brain disease), as this approach may point to new targets for treatment. As GBA1 mutations are also a major risk factor for developing Parkinson's disease, what is learned from studying nGD may also help prevent, ameliorate or reverse the loss of dopaminergic neurons in Parkinson's disease.

Reprogramming Technology

A major difficulty to study the pathological events leading to nGD is that neurons from patients harboring GBA1 mutations have not been available. To circumvent this problem, our laboratory has used a novel reprogramming technology developed by Shinya Yamanaka, 2012 Nobel Laureate, which enabled us to generate these precious neurons from GD patients. In a process akin to biological alchemy, by introducing four reprogramming factors into fibroblasts obtained from skin biopsies of patients affected by all clinical subtypes of GD, we generated a panel of induced pluripotent stem cells (iPSC), with coverage of some of the most frequent GBA1 mutations, including

GBA1 is the gene that when defective causes Gaucher disease

Neuronopathic Gaucher disease (nGD) is a devastating disease that affects infants, and is caused by severe mutations in the GBA1 gene. GBA1 encodes an enzyme called glucocerebrosidase. The enzyme deficiency in GD results in the accumulation of the lipid glucosylceramide and other metabolites in the lysosomes of cells, impairing their function in a

"OUR LABORATORY IS VERY GRATEFUL TO THE CGRF FOR GENEROUS FUNDING THAT WILL ENABLE US TO FIND ANSWERS TO THESE IMPORTANT QUESTIONS."

number of tissues including liver, spleen, bone marrow, bone, and brain. The development of Enzyme Replacement Therapy (ERT) for GD was made possible by seminal studies by Dr. Roscoe Brady at the NIH (see Summer 2016 Newsletter). Dr. Brady identified the genetic defect in GD as mutations in glucocerebrosidase, and made the critical observation that uptake of the therapeutic enzyme by Gaucher macrophages was facilitated by trimming some of the sugars in the enzyme preparation used for treatment.



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CLINICAL RESEARCH ON GAUCHER DISEASE TYPE 3



Raphael Schiffmann M.D., M.H.Sc.
Baylor Research Institute
Chairman – CORF Scientific
Advisory Board

Gaucher disease type 3 is the chronic form of neuronopathic Gaucher disease. It may present in infancy, childhood or even in adulthood. Neuronopathic Gaucher is estimated to be present only in 5% of the Gaucher patient population in Western countries such as the US and Europe. However, scientific publications suggest that many if not the majority of patients with Gaucher disease in non-European countries such as China, Egypt, India, Japan, Taiwan, and Korea have Gaucher type 3 (where the brain is affected). Since there is not yet a satisfactory therapy for the neurological manifestations of Gaucher disease, and substantial numbers of Gaucher disease patients around the world are medically underserved.

Two main therapeutic approaches are being developed at present.

Trial #1: LEAP - sponsored by Sanofi Genzyme

The first is a treatment trial directed at the primary problem in Gaucher type 3, which is the accumulation of the fatty molecule glucosylceramide in the brain. It is an initial study of a new oral drug designed to reduce the production (synthesis) of glucocerebroside (the fatty substance). This therapeutic method is often referred to as 'substrate reduction therapy' or SRT. There is already on the market an FDA approved SRT medication for Gaucher disease that is called eliglustat. However, eliglustat does not enter the brain and therefore cannot be used to treat neuronopathic Gaucher disease. The new study is called GZ/SAR402671 in Combination With Cerezyme in Adult Patients With Gaucher

"IT IS HOPED THAT THE STUDY WILL LEAD TO BETTER PREDICTION AND TREATMENT OF THE VARIOUS NEUROLOGICAL COMPLICATIONS OF GAUCHER DISEASE."

Disease Type 3 (LEAP), is sponsored by Sanofi Genzyme and is described on the clinicaltrials.gov web page: <https://clinicaltrials.gov/ct2/show/NCT02843035>

This is a two-part study. Part 1 is a patient visit consisting of a number of clinical tests designed to see if the patient will qualify for the treatment trial itself. The second part of the study is the actual treatment trial of the study drug GZ/SAR402671. Participation in part 2 will last approximately 15 months and includes 6 clinical visits. Patients eligible for part 2 will receive study drug for 12 months. For some study visits patients may be required to stay overnight to complete all of the tests and procedures.

"...WHY SOME PATIENTS DEVELOP NEUROLOGICAL SYMPTOMS, WHILST OTHERS DO NOT, REMAINS TRULY PUZZLING."

A patient with Gaucher disease type 3 may be eligible to participate in LEAP if one:

- Is 18 years or older
- Has Gaucher disease type 3 (must complete part 1 to participate in part 2)
- Has received treatment with enzyme replacement therapy for at least 3 years and received Cerezyme (Imiglucerase) at a stable dose for the past 6 months.

Trial #2: Do individual genetic variations influence the development of neuronopathic Gaucher disease?

The second therapeutic approach is an international collaboration to identify genetic variations that explain why patients with Gaucher disease type 3 can have vastly different clinical disease severity despite having the same mutation of their GBA1 gene – 'the Gaucher gene'. The study is called: Do individual genetic variations influence the development of neuronopathic Gaucher disease?

Despite the very significant advances achieved in understanding Gaucher disease, the reason why some patients develop neurological symptoms, whilst others do not, remains truly puzzling. Recently, researchers in Israel (Drs. Andy Klein and Tony Futerman) have found some candidate genes implicated in a laboratory model of Gaucher disease. These and other genes are likely to affect the development and severity of neuronopathic Gaucher disease.

Drs. Nicholas Smith and Timothy Cox from the Department of Medicine, University of Cambridge and Addenbrooke's Hospital, are the Chief Investigators of this study. This study will be initiated this year. Physicians from the US, Europe, Asia, Australia and Africa will provide anonymous DNA samples from patients with Gaucher disease who are homozygotes for the most common Gaucher disease type 3 mutation – L444P. Detailed clinical description of the patients will also be provided. This study will attempt to identify changes in various genes that explain why some patients with the same mutation are very mild and others are severe. It is hoped that the study will lead to better prediction and treatment of the various neurological complications of Gaucher disease. ■



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OR

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