# Summer 2006 HELPING HANDS

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

## THE ONLY THING INCURABLE IS OUR PASSION.



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Dennis Tyler Cooper Doran Jr.

Lauren Rvan Cameron Kristina Madeline Robert Marsh lames Conklin Watson

When a cure is

found it will indeed

not be ... "entirely

by accident".

Grant & Hannah Emma C Colwell Pozzobon Collin Garrett Geven



**Gregory Macres** 

Chairman/Founder

"I never did anything worth doing entirely by accident...Almost none of my inventions were derived in that manner. They were achieved by having trained myself to be analytical and to endure and tolerate hard work". - Thomas Edison On June 23-25, 2006 the Children's Gaucher Research

Fund and the National Institutes of Health hosted the 2nd Lysosomal Diseases and the Brain" conference in Sacramento, California. In attendance were over 100 researchers,

(M.D.'s and PhD's) from ten different countries. The conference attracted medical researchers from America, Brazil, Canada, England, France, Germany, Israel, Italy, Korea, Sweden and Switzerland.

The conference began with a reception dinner on a beautiful summer evening at the Sacra-

mento river-front Rio City Café. Dr. Elsa Shapiro provided a Tribute to the Late Dr. William Krivit, who was little **Deborah**<sup>#</sup>**Macres R.N.** Gregory's (our son) Bone Marrow Transplant doctor. Dr. Krivit was a dedicated man who attended the first Lysosomal diseases and the Brain conference in Bethesda Maryland, and surely would have attended this one.

The conference resumed on Saturday morning with two full days of scientific research presentations. Researchers representing some of the most respected scientific research laboratories in the world shared cutting edge research on the brain. The goal of the conference was to share the latest research, create cross-pollination of ideas between institutions, and foster collaborations that will move us closer to our ultimate goal – Finding a Cure.

For a non-scientist, standing among this group is a humbling experience. These are brilliant people, people who are "trained", who are "analytical", and who "tolerate hard work". When a cure is found it will indeed not be ... "entirely by accident".

For those of us who do not participate in these academic pursuits, our role is different, but equally important.

Whether it is your words of encouragement, your donation of time and talent, or your donation of funds for research; collectively, we all play a role. By joining hands you are lending a Helping Hand – offering hope to those children whose lives have been curtailed by disease. We appreciate all that you do!

# A Tribute

Dr. William Krivit (University of Minnesota) passed away on December 8, 2005, at the age of 80. Dr. Krivit was world-renown in the field of lysosomal diseases. He was known for his humanism and strong advocacy for his patients (and all children, especially those who were disadvantaged), and internationally for his academic work, his leadership, his innovation, and the passionate pursuit of his ideas He will be missed







Suboral Mores Founder



# **Conference: Lysosomal Diseases and the Brain** June 23-25, 2006 Sacramento, California



# **Treatment of Gaucher Disease** A Historical Perspective

Excessive amounts of a fatty substance called glucocerebroside accumulates in organs and bones of patients with Gaucher disease causing enlargement of the spleen and liver, damage to bones, anemia and low blood platelets. In 1965, the metabolic defect in Gaucher disease was shown to be a deficiency of the enzyme glucocerebrosidase. This enzyme is necessary for the biodegradation (breakdown) of glucocerebroside that arises from the turnover (death) of senescent red and white blood cells. In 1966. I proposed that supplementing or replacing the deficient glucocerebrosidase might be helpful for Gaucher patients. I wanted to use a human tissue as source of this enzyme, and it occurred to me that human placenta might be useful. My colleagues and I discovered that four sugar side chains. We targeted it to macrophages by using enzymes to remove the three outer components of the side chains exposing the sugar mannose. In the first clinical trial with mannose-terminal glucocerebrosidase, only one of the eight recipients, a 5 year-old boy, experienced benefit. We conducted a dose-response trial to learn how much glucocerebrosidase was required to obtain consistent reduction of stored glucocerebroside. Using that dose, we carried out a trial with 12 patients with type 1 (non-neuronopathic/non-brain) Gaucher disease. All of the recipients showed increased hemoglobin and blood platelets, reduction of the size of their spleen and liver and improvement of their bones.

The FDA approved macrophage-targeted glucocerebro-

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placenta does have the enzyme, but it was hard to purify it from this source.

We eventually obtained small amounts of it and found that intravenous injections of glucocerebrosidase (the replacement enzyme) caused a reduction of accumulated glucocerebroside (left over dead cells that should be cleared from the body) in the liver. Injections of glucocerebrosidase obtained in this fashion gave inconsistent results because it was not directed to cells (macrophages) in which glucocerebroside (fatty substance) is stored. We then learned that the enzyme was a glycoprotein that had

sidase (Enzyme Replacement Therapy) for patients with Gaucher disease in April 1991, thus providing the first successful treatment for thousands of Gaucher patients. Unfortunately, intravenously administered enzymes do not reach the brain in children who have the neuronopathic form (brain involvement) of Gaucher disease. For medical researchers the "Lysosomal Diseases and the Brain" conference was a unique opportunity where novel strategies were discussed to develop therapies for patients with Gaucher disease and other hereditary disorders where the brain is involved.



#### Roscoe O. Brady M.D Scientist Emeritus

Developmental and Metabolic Neurology Branch National Institutes of Health Bethesda, Maryland

## **Lysosomal Diseases** The Basic Science

Basic science refers to the work done in the laboratory in studying a particular biological process or disease. This type of research is absolutely crucial to understand the consequence of an inbom error of metabolism such as a lysosomal storage material with specific proteins is likely to lead to the development of new therapies for the lysosomal disorders that affect the brain. For that, the creation of animal models is critical. At the conference, a number of exciting new animal models that

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disease and to develop novel approaches to therapy. In the past, people thought that the storage material (cells that are not cleared from the body) that consists mostly of fatty molecules (lipids) simply "strangles" the brain cells in a non-specific way and prevents them from functioning normally. Investigators presenting in this conference, each working on different disorders, showed that the storage materials in each disease have different and specific effect on brain cells. Interestingly, each storage molecule selectively affects a different protein that uses ionized calcium to signal other molecules. Most of these proteins are called ion channels or ion transporters. Excessive activation or inhibition of such proteins by the accumulating lipid leads to different negative consequences to brain cells causing them to malfunction or die. This is one fundamental explanation for marked heterogeneity of clinical characteristics of these diseases.

In turn, some proteins thought to be ion channels can cause lysosomal brain diseases. The understanding of the precise interaction of the storage mimic the neurological involvement of Gaucher disease were presented for the first time.

A wonderful example of how basic science alone led to the discovery of the mechanism of disease and a new therapy is the example of Marfan syndrome. Investigators from Johns Hopkins University School of Medicine lead by Dr. Harry C. Dietz discovered, after many years of misconception in this field, the correct mechanism for the deadly aortic enlargement in this disorder. That finding led to their discovery, in the animal model for Marfan syndrome, that a known safe and already FDA-approved drug (losartan) can completely prevent the progressive enlargement and rupture of the aorta. Clinical trials on patients with this drug have been initiated.

The new findings presented at the "Lysosomal Diseases and the Brain" conference together with the crucial scientific exchanges that the investigators had during the meeting, are likely to generate research leading to novel therapeutic approaches for the large number of lysosomal diseases that affect the brain.

#### Raphael Schiffmann M.D.



Chief, Clinical Investigations Developmental and Metabolic Neurology Branch National Institutes of Health Bethesda, Maryland

#### Over the past 15 years Gaucher disease has been the prototype for lysosomal disease clinical care, and advances in research

Therapy Options for the Brain

care, and advances in research and development of therapies. The clinical and economic success of enzyme replacement therapy (see Roscoe Brady M.D. article above) for Gaucher disease type 1, non-neuronopathic, has provided the impetus for creation of enzyme therapies for five other lysosomal diseases that improve the health of affected patients. In addition, this success has stimulated continuing research and develop-

Lysosomal Diseases

inaccessible to all peripherally administered therapies, except some limited successes with bone marrow-derived stem cell transplantation. The newer strategies are based on small molecules and genes that can alter production of the pathologic substrate (substrate synthesis inhibition) or improve the function of the abnormal enzyme in patients (pharmacologic chaperones), and gene therapy, respectively. Furthermore, additional therapeutic strategies are directed to diminishing the detrimental effects of the

"Importantly, these newer strategies could have significant impacts on the majority of lysosomal diseases that involve the central nervous system..."

ment of newer approaches to therapies that should provide in the near future alternative/ supplementary treatments for Gaucher disease and the other lysosomal diseases.

Importantly, these newer strategies could have significant impacts on the majority of lysosomal diseases that involve the central nervous system (brain), a compartment that has been concomitant proinflammatory responses that occur in patients with lysosomal diseases.

Progress in research and implementation of each of these approaches was highlighted at the "Lysosomal Diseases and the Brain" conference, and indicate the current successes and future hopes for afflicted families with the lysosomal storage diseases.



#### Gregory Grabowski M.D.

Director, Division and Program in Human Genetics University of Cincinnati Cincinnati, Ohio



## **Lysosomal Diseases** The Basic Science

"The similarities between Neuronopathic Gaucher Disease and the Lewy body dementias are so great that therapy for Neuronopathic Gaucher Disease may impact Diffuse Lewy body disease, the second most common cause of dementia in ease patients have a remarkably high incidence for the Gaucher disease allele. Ongoing research to safely shuttle effective therapeutic agents through the blood brain barrier, coupled with an already highly effective systemic enzyme replacement therapy

"At the conference, a number of exciting new animal models that mimic the neurological involvement of Gaucher disease were presented for the first time."

the world. Thus, the monies spent on one disease may have an even greater impact upon a more prevalent scourge of mankind."

The Lewy body dementias or a better term "synucleinopathies" are neurodegenerative diseases that have abnormal accumulation of synuclein in neurons such as Diffuse Lewy body disease and Parkinson's disease with dementia. Since the above statement was made a few years ago, there has been a wealth of progress with several groups of researchers elucidating the biochemical, genetic, epidemiological evidence; linking Gaucher disease of all types, carriers of the mutation, and even in patients with polymorphisms of the Gaucher gene with "Gaucher associated Synucleinopathy with Parkinsonism and Dementia''. In population studies in the USA and Israel, Parkinson's Disand continuing research on Gaucher disease, Parkinsonism and Dementia will impact not only the Gaucher disease patient, but their family members who carry the Gaucher allele, and unsuspecting carriers of the Gaucher gene or polymorphism who have a family history of Parkinson's disease and/or dementia.

The Children's Gaucher Research Fund has been a vital platform fostering scientific collaboration and discussion, bringing together devoted Gaucher disease family members, dedicated researchers, and charitable financial contributors. With so great an effort on behalf of all those involved, it has to be just over the horizon that Neuronopathic Gaucher Disease may be effectually treated, and alongside, Lewy Body Dementias, finally countered, the first of the neurodegenerative diseases to have an effective treatment.



Col. Kondi Wong M.D. USAF MC Chief, Division of Neuropathology Wilford Hall Medical Center Lackland, Air Force Base San Antonio, Texas

## Importance of the CGRF

In 1974, when Dr. Christian de Duve received the Nobel Prize, he wrote that 'the mysterious chapter of the pathology of congenital lysosomal enzyme deficiencies has been largely elucidated'. That being the case, why did over a hundred scientists from more than ten different countries meet over the weekend of 24 and 25 June in Sacramento for the CGRF's 2nd international conference on 'Lysosomal diseases and the Brain'? Of course Dr. Duve was not wrong - in fact he was, and still is, a brilliant scientist, but his family of diseases, and the second addressed new and novel therapeutic approaches. A cure for neuronopathic Gaucher, and other diseases in this family, will not be found quickly, and will require years of dedicated research by many of the people who attended this conference.

As I see it, the conference serves a number of purposes that are not met by any other similar meeting. It helps facilitate collaborations amongst the leading scientists in this area, discusses groundbreaking research, and is undoubtedly one

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discovery of the metabolic diseases associated with lysosomal enzymes was only the beginning of a long road. Indeed, the meeting in Sacramento, to which Dr. de Duve was invited, but unfortunately could not attend, was testimony not only to the progress that has been made over the past few years, but also to how much still remains to be discovered.

The conference was divided into two major themes, the first being the pathology of the lysosomal storage diseases, including type 2 and 3 Gaucher disease, with a view to understanding why and how the brain is affected in this devastating

of the best, or the best conference on this subject anywhere. It is unique in that it brings together not only scientists focused on research, but parents of affected children and those who care for them, both physicians and nurses, which gives an additional valuable perspective both to those who work in basic research and those personally affected by these devastating diseases. I believe that the CGRF and its donors deserve much credit for hosting this flagship conference, and for having the vision to understand that advances in medical science are all based on advances in basic science.



#### Tony Futerman Ph.D.

Professor Department of Biological Chemistry Weizmann Institute of Science Rehovot, Israel

## first step in

res and <u>many</u>

THE ONLY THING

# Wow! What Can You Say



**THANK YOU** does not seem to be enough for Carol Black who does so much for the Children's Gaucher Research Fund. For 5 years running Carol has organized the Coldwell Banker Charity Golf Tournament in Sacramento California, an event that gets better each and every year. In addition to that, Carol

It is because of these efforts from our talented volunteers like Carol Black, that we are able to continue our commitment:

is our Conference Coordinator, who organized and coordinated the terrific "Lysosomal Diseases and the Brain" conference that occurred this summer in Sacramento. It is because of these efforts from our talented volunteers like Carol Black, that we are able to continue our commitment: That 100% Of Every Donation Will Go to Medical Research.



# **Sheldon High School Awake-A-Thon**

High school Senior Tu Tran, Immediate past Lieutenant Governor (Key Club) and President of the National Honor Society organized the Sheldon High School Awake-A-Thon that took place in May of 2006. Modeled after the Awake-A-Thon's at Florin High School (noted in past newsletters) Tu Tran displayed his ability to organize and motivate his fellow students. Witnessing this event with some 250 young men and women truly gives you faith in the future leaders of America. High Schools Participating Include: Bella Vista, El Camino, Folsom, Loretto, Mira Loma, Oakridge, Pleasant Grove, Rio Americano, Sheldon, Florin, Franklin, Laguna Creek, Woodcreek, John F. Kennedy, Davis, McClatchy, River City, Sacramento, Monterey Trails.





June 19, 2006 marked the Fifth Annual Coldwell Banker Sacramento Charity Golf Tournament benefiting the Children's Gaucher Research Fund, held at Valley Hi Country Club in Elk Grove. Nearly 200 golfers, volunteers and dinner guests gathered on a beautiful summer day for a barbeque lunch and putting contest, followed by 18 holes of golf, dinner and a live auction.

### In Loving Memory of Brenna Morgan Laws



**"Our Beautiful Brenna Girl"** August 6, 2004 to March 20, 2006 Castaic California

### In Loving Memory of Nadia Alassandra Landin



**"We will always love you our lil Princess"** December 1, 2004 to December 24, 2005 Modesto California

## In Loving Memory of Abigale Dianne Berweiler



**"In Loving Memory of our Little Angel"** December 8, 2002 to October 24, 2003 Wauwatusa Wisconsin

## 100% To Research

You need to know:

- I. 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:

Children's Gaucher Research Fund P.O. Box 2123 Granite Bay, California 95746-2123

# Children's Gaucher Research Fund



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