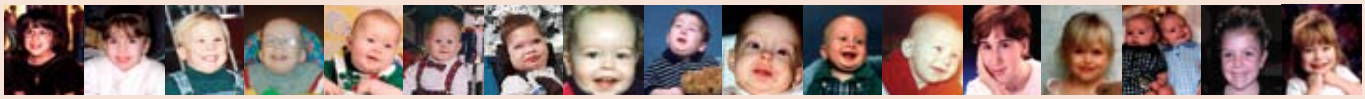
Summer 2008

HELPING HANDS

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



Valerie Yannias | Victoria Casares | Gregory Austin Macres | Noah Jerome Shaffer | Kyle Herrel | Jared Patrick Ashley | Joseph DeFacci | Andrew Dennis Doran Jr. | James Tyler Cooper | Lauren Marsh | Ryan James Conklin | Cameron Robert Watson | Kristina C. | Madeline Collin | Grant & Garrett Geyer | Danielle Loncharich | Emma C. Pozzobon

THE ONLY THING INCURABLE IS OUR PASSION

In the beginning the goal of the CGRF was to find a cure for Gaucher disease type 2, a rare lysosomal disease that took the life of our son Gregory. However this journey has widened its scope and broadened its impact well beyond our wildest dreams. Research that has been funded by the CGRF has found a strong commonality among all neuronopathic lysosomal diseases (of which Gaucher is one) that affect the brains in young children. There is no cure for these diseases, the vast majority effect very young children, and although the severity levels and time of onset differ the majority of children pass away at a young age. It is now believed that a cure for one will lead to a cure for some 26 lysosomal diseases that affect the brains of young children. Combined, the prevalence of these diseases is 1:6000 births, a greater prevalence than Cystic Fibrosis and Muscular Dystrophy.

> **"Combined, the prevalence of these diseases is 1:6000 births, a greater prevalence than Cystic Fibrosis and Muscular Dystrophy."**

This led us in 2002 to organize our first scientific conference entitled "Lysosomal Diseases and the Brain". At the end of May, 2008 our third Lysosomal Diseases and the Brain conference (www.lysosomal-brain-conf.org) attracted 126 scientific researchers from 10 different countries. This unprecedented forum allowed over 120 related medical experts from 10 different countries an opportunity to share information, collaborate, and explore new ideas leading to a cure of neuronopathic lysosomal diseases. It has been amazing to see that the death of one brave little boy could lead to world-wide collaborations in an effort to save children from this devastating set of diseases. Our quest is now to find a cure for all 26+ neuronopathic lysosomal diseases that affect the brains of children.

It should be noted that these conferences, as important as they are, are not funded by your donations. Funds to support these conferences are derived from companies who have an interest in supporting and attending these conferences. If the expenses for the conference exceeds the revenue received from corporate support (as was the case in May, 2008) Greg and Deborah Macres pay the difference. The following is an email received after our May, 2008 conference:

Dear Greg and Deborah,
I wanted to thank you for the opportunity to participate in this incredible conference - the science and the bold vision of the investigators took my breath away. What you have started with participation of other families has ushered in an extraordinary momentum that will have far reaching consequences of lasting value, not just for Gaucher's disease but for other devastating lysosomal diseases as well. I felt privileged to be part of this wonderful way to honor Gregory and all the extraordinary children who have suffered from these conditions. I came away feeling certain that the work you have help start will lead to effective treatments.

With great affection,

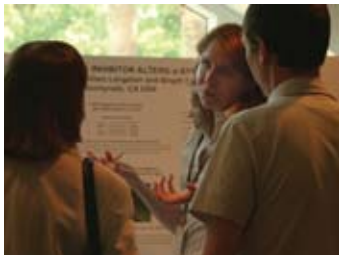
Pram
Pramod K. Mistry MD, PhD, FRCP,
Professor of Pediatrics and Medicine,
Chief, Section of Pediatric Hepatolo and Gastroenterology
Yale University School of Medicine

Gregory Macres
Chairman/Founder

Deborah Macres R.N.
Founder

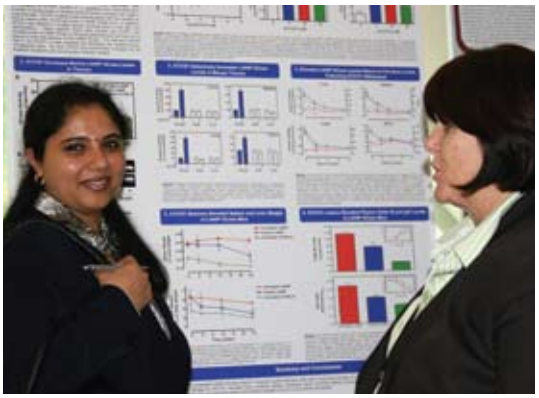
Inside this Issue...

2008 Conference:
Lysosomal Diseases and the Brain



The Basic Science

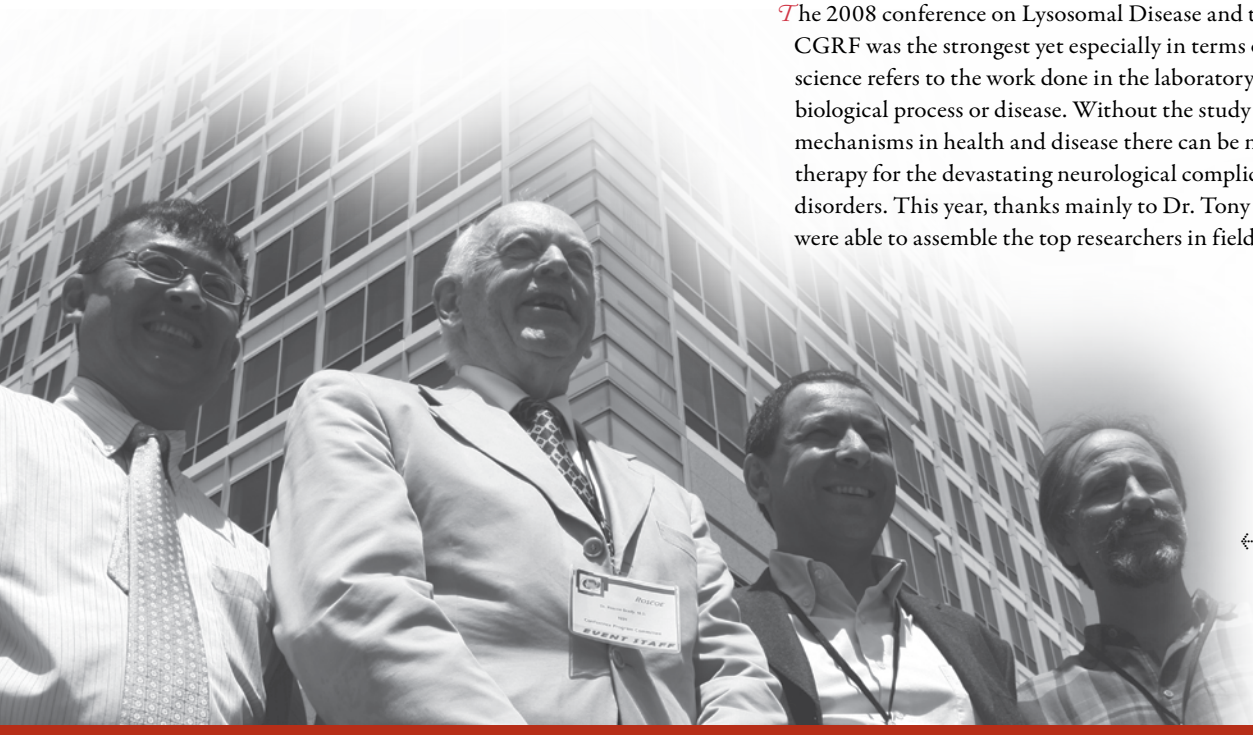
By Raphael Schiffmann M.D.



Poster Session

Speakers and Poster Board Presenters

The 2008 conference on Lysosomal Disease and the Brain sponsored by the CGRF was the strongest yet especially in terms of the basic science. Basic science refers to the work done in the laboratory in studying a particular biological process or disease. Without the study of the basic biological mechanisms in health and disease there can be no hope of an effective therapy for the devastating neurological complications of the lysosomal disorders. This year, thanks mainly to Dr. Tony Futerman's efforts, we were able to assemble the top researchers in fields related to lysosomal dis-



Conference Program Committee:
from right to left – Dr. Kondi Wong, Dr. Roscoe Brady – Dr. Tony Futerman
Dr. Raphael Schiffmann

Lysosomal Diseases and the Brain

May 29-31, 2008 ⋯ Sacramento, California

orders. The term 'related' is important since many of these investigators do not have a long history in lysosomal diseases themselves. However, they are experts in different cellular problems such as the making and breaking down of the lipids (fatty molecules) of the cell, or the function of the parts of the cell that are commonly abnormal in lysosomal disease such as the lysosome. We heard impressive lectures from investigators that came to the field of lysosomal disease from general neuroscience and made great strides in their research because they were able to look at these diseases from a fresh vantage point. Very often the fresh approach led to completely novel therapeutic approaches. For example, Dr. Jonathan Cooper and colleague discovered that there is an immune problem in neuronal cell lipofuscinosis for Batten's disease. Using this information he was able to markedly improve the health of the mouse models of the disease with a medication that improves the body's immune regulation.

"…we were able to assemble the top researchers in fields related to lysosomal disorders."

Another important theme this year was the importance of studying the earliest phase of disease process and of starting therapy at the earliest possible stage of the illness. Again, basic science shows the way. Dr. Fran Platt and many other investigators have been studying Niemann-Pick disease type C for many years without obtaining a full understanding of the mechanism of the disease or even which molecules are responsible for the damage to the neurons in the brain. Dr. Platt and her colleagues recently looked at the earliest (not necessarily the largest) possible molecular abnormality occurring in Niemann-Pick C and discovered that sphingosine, a fatty alcohol, becomes elevated first. This discovery in cells and animal models of the disease opens a new therapeutic approach that is very promising and is designed to decrease sphingosine levels in the brain or to decrease the negative consequences of sphingosine in the cell. Other investigators testing different therapies in the cells and animal models all found that the earliest one initiates therapy the better the result.

Therefore, our conference this year demonstrated through excellent basic and laboratory science that early intervention in lysosomal disease, and probably other genetic diseases that affect the brain, are the way to go. These findings further raise the importance of screening for these diseases in order to identify patients who are still asymptomatic but likely to develop severe brain diseases at a later age.

"It was a great meeting. I was delighted with the curriculum and the presentations. I feel honored and fortunate for your generosity. I will be more than happy to be on the list to contribute to your foundation on an annual basis. Please keep this amazing dream going, it's truly remarkable."

Katherine Bianco, M.D. Maternal-Fetal Medicine
{ Medical Genetics } University of California San Francisco (UCSF).

Potential Therapies

By Roscoe O. Brady, M.D.

The Lysosomal Diseases and the Brain conference was truly outstanding! In addition to Gaucher disease, more that 26 other hereditary metabolic storage disorders seriously affect the brain. Each is caused by a deficiency of an enzyme required for the normal turnover of various lipids, carbohydrates and proteins. These materials must be biodegraded, otherwise toxic quantities accumulate and impair brain function.

Enzyme replacement therapy (ERT) is now standard care for patients with Type 1 Gaucher disease without brain involvement. Novel procedures must be developed to enable therapeutic enzymes to cross the blood-brain barrier (BBB). A novel approach to this goal was presented by Dr. William Pardridge. He and his colleagues linked an enzyme to an antibody to the insulin receptor located on the inner surface of cells that form the BBB. This complex transported across the BBB from the blood into the brain. A different strategy is under development by Dr. Francis Choy in which a short sequence of amino acids called TAT is attached to enzymes to achieve the same goal. How soon these approaches will be tried in patients is uncertain, but novel and potentially beneficial strategies to enzyme therapy to treat patients with involvement of the central nervous system (CNS) continue at this time.

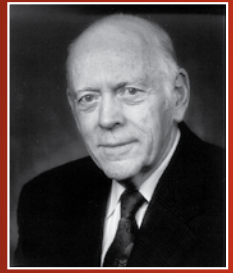
"In addition to Gaucher disease, more that 26 other hereditary metabolic storage disorders seriously affect the brain."

Another strategy called substrate reduction therapy using small molecules to block the formation of accumulating materials appears to offer considerable potential. An update of this approach was presented by Dr. Fran Platt from Oxford University. Molecular chaperone therapy, in which mis-folded enzymes are directed to lysosomes in cells where they function properly, was discussed by Dr. Brandon Wustman and Dr. Jeffrey Kelly. An update of the potential of gene therapy for CNS disorders was presented by Dr. Seng Cheng.

An aspect concerning treatment of the brain in metabolic disorders that was not extensively discussed was direct intracerebral injection of enzymes. Repeated intrathecal (spinal canal) injections are being tried in animal models of storage disorders, but there are obvious hazards using such an approach to treat humans.

All of the participants truly believe the conference provided a superb forum and that much additional benefit was derived from one-on-one exchanges between participants. All strongly felt that the series most definitely should be continued.

Raphael Schiffmann M.D.
Director, Institute of Metabolic Disease
Baylor Research Institute
Dallas, Texas



Roscoe O. Brady, M.D.
Scientist Emeritus
National Institutes of Health
Bethesda, Maryland

Gaucher disease and Parkinsonism

By Kondi Wong, M.D.

The Lysosomal Diseases and the Brain Conference held in Sacramento California and hosted by the Children's Gaucher Research Fund continues to be a remarkable success story, not only in terms of conference enrollment, but as a symposium of current, ongoing scientific research where researchers can present and critique the latest scientific discoveries, understand the direction of research initiatives and formulate a series of investigations over the next 2 years...until the next LBD conference in Sacramento.

"The Lysosomal Diseases and the Brain Conference … continues to be a remarkable success story…"

In the 1999-2001 time frame, genetic and clinicopathologic descriptions of Gaucher disease associated synucleinopathy and Parkinsonism were forwarded by Dr. Ellen Sidransky and Dr. Raphael Schiffmann. A patient with Type 1 Gaucher disease and Parkinson's disease was described even earlier, in 1986, by Dr. Ari Zimran. At that time, few people, other than Tony Futerman, were addressing the biochemical mechanisms of the link between the more common neurodegenerative diseases, Diffuse Lewy body Disease (the cause of 20% of all dementias the 2nd most common cause after Alzheimer's) and Parkinson's disease (affecting over 1.5 million in the US) and Gaucher's disease. Indeed, the link between Gaucher disease and Parkinson's disease was disputed at the 2006 LBD Sacramento conference.

Fast forward to 2008; Researchers in the US and world wide have corroborated the Gaucher mutation as a risk factor for Parkinson's disease (PD); increasing the risk for PD nearly 5 fold. Researchers at the Sacramento LDB conference, presented evidence of the role of glucosylceramide, the lipid that accumulates in Gaucher disease, in the regulation of ion channels, lipid metabolism, lysosomes, other lipid vesicles and in the aggregation of synuclein, which accumulates in cortical and brain stem Lewy bodies in Diffuse Lewy body disease (DLBD) and Parkinson's disease. Modulation of glucocerebrosidase (the enzyme affected in Gaucher disease) by "chaperones" (chemical and pharmaceutical modulators) appears to enhance its activity and reverse the synuclein metabolic derangement and synuclein aggregation suggesting that pharmaceutical agents in the future may be able to reverse the neurodegenerative changes in Gaucher disease, other lysosomal disorders and more common neurodegenerative diseases, Parkinson's and Diffuse Lewy body disease.

Importance of the Conference

By Tony Futerman Ph.D.

The recent 'Lysosomal Diseases and the Brain' conference in Sacramento was a spectacular success, combining, as in the previous conference, basic science with new therapeutic approaches. The two questions that the conference attempted to address were:

(i) Why does accumulation of metabolites in lysosomes cause disease, and specifically neurological disease, and what are the underlying molecular and cellular mechanisms?

(ii) What new therapeutic approaches might arise out of the basic science?

These questions were addressed over two days in intense and stimulating discussion, in which some of the leading researchers in the area of lysosomal storage diseases participated. Moreover, in the 2008 conference, there was a renewed emphasis on bringing new researchers into this field. Thus, a talk was given on glucosylceramide biology (glucosylceramide is the metabolite that accumulates in Gaucher disease), on lysosome biology, and on autophagy – none of these areas had been addressed in previous conferences. In addition, significant discussion was devoted to mouse models of neuronopathic Gaucher disease and to disease pathology in other related lysosomal storage diseases.

"…this conference has become the best conference in the field of lysosomal storage diseases"

The talks were at the highest level, given by leaders in the field, and the discussion was exciting and helped define a number of putative novel research directions. My feeling is that this conference has become the best conference in the field of lysosomal storage diseases. This is both due to the excellent level of the talks and discussion, but also by the fact that the Children's Gaucher Research Fund gives the scientific organizing committee, of which I had the honor to chair, complete freedom to invite whoever they deem most worthy to attend and speak at this meeting, in a totally science-driven manner. I believe this makes the conference unique among those in this field, and I congratulate the CGRF for having the vision to understand that basic science is the first step in finding a cure for these lethal diseases. Roll on 2010!

Kondi Wong, M.D.
Professor of Pathology
University of South Florida Medical School
Tampa, Florida

Tony Futerman Ph.D.
Professor
Department of Biological Chemistry
Weizmann Institute of Science
Rehovot, Israel

Florin High School Students

"Raise Over $50,000 in 6 Years"

My name is Cari Yang, the President of Florin High Key Club for the 2008-2009 academic year. I first joined Key Club my freshmen year, and was inspired to join because of my sisters and brothers - dedicated members of the club during their high school years. I learned that by volunteering, an individual can make a difference, and that people working together can make a bigger difference. My Key Club experience is not rare, but common amongst my peers, because I see their selfless service everyday.

Seeing others like myself, volunteering to make a change in the community made me realize that I could do the same. Our club has been hosting an annual event during the fall semester called, the Key Club Awake-A-Thon, which raises money and awareness for the Children's Gauchers Research Fund. This event has shown me just how powerful a small group of high school students can be. This past year alone, we surpassed our previous club record my raising more than $13,000 dollars for the Children's Gauchers Research Fund. When I found out how much money we raised, I was blown away!

Key Club is the greatest organization that I have ever been a part of because it opens doors to opportunities that are not offered to teenagers anywhere else. The club provides me with the opportunity to become a leader and it helps me motivate others like myself. Nevertheless, now that I have been selected by my peers to lead the club, I will give it all I have and I will carry on with our tradition of serving our home, school, and community. The Key Club Bee's always serve with spirit!

Cari Yang, President 08-09
Mr. Elias Mendoza, Advisor
Florin High Key Club, Division 7

Carol Black Selfless Devotion

Carol Black

IT'S JUNE 24TH, AND MY FEET ARE KILLING ME; not only that but my head is still spinning from yesterday's non-stop activity directing our Seventh Annual Coldwell Banker Charity Golf Tournament. The last several months spent coordinating two large scale events on behalf of the CGRF have been sheer madness, but it's by choice and I honestly wouldn't have it any other way.

In early 2002, I was asked to put together a charity golf tournament for Coldwell Banker as part of philanthropic community efforts with all proceeds benefiting a local charity. Our sister offices in the Silicon Valley have been also coordinating their own golf tournament for several years- the Gregory Austin Macres Memorial Tournament- and after speaking with their committee and reviewing the background of the Children's Gaucher Research Fund, it was an easy decision that ours too, would benefit the CGRF. Although I have an event planning background, for someone who has never set foot on a golf course, the first golf tournament was an enlightening and exhausting experience! Yet with 144 golfers and net proceeds of around $12,000 many would consider it a success- now seven years and hundreds of golfers later, and forcasting to surpass $120,000 in net donations, the annual tournament is one of the most popular of our corporate events. I love planning the tournament; not only for the excitement, but also because I get to witness selfless generousity of others. The event is running like a well-oiled machine, but it couldn't be so without a troop of dedicated volunteers and generous sponsors, most of whom return year after year and ask nothing (except perhaps a fun day of golf!) in return. Thanks to our committee and volunteers each facet just comes together beautifully and the end result is that our organization had a fun day golfing for a great cause!

Although this began as a work project, now it has grown to something larger; something for me to feel like I can be a part of; it became more than "work" after I've gotten to know Greg and Deborah and their family personally. I can't imagine how difficult it is to lose a child, but I'm inspired by the way that they've turned their personal tragedy into a mission to benefit other families. The thought that someday there WILL be a cure and knowing that our event promotes the CGRF to individuals who haven't ever heard of Gaucher disease is the reason that our tournament committee strives to make each event better than the last. I'm honored to be a part of the CGRF family; and each time I hear Greg talk about little Gregory during one of the event banquets, it makes every second of time that I spend coordinating a fundraising event or medical conference worthwhile.

Wells Fargo Supports the CGRF

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

Research Update: As discussed in the Summer, 2007 newsletter the Scientific Advisory Board for the CGRF reviewed seven research proposals. Three of these were approved and sent for peer review by three researchers outside the Scientific Advisory Board. Only one received an anonymous recommendation and was funded in the fall of 2007. The CGRF is now increasing its funding commitments and is in the process of reviewing further scientific proposals in the summer of 2008.

In Loving Memory of

Savannah Grace Buie

"Our Daughter - a gift from God who taught us about Life, Love, and Faith."

November 4, 2006 to July 9, 2007
O'Fallon, Missouri

Children's Gaucher Research Fund

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