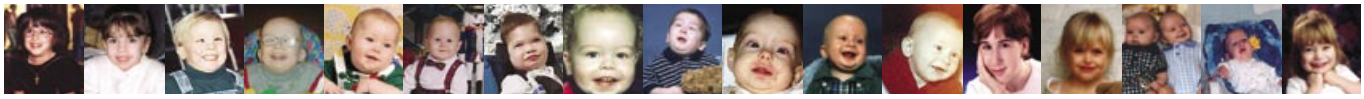
Winter 2005-2006

HELPING HANDS

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

THE ONLY THING INCURABLE IS OUR PASSION.



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 | Madeline Collin | Grant & Garrett Geyer | Hannah Colwell | Emma C. Pozzobon

When the Children's Gaucher Research Fund began we had a simple goal; to find a cure for a rare orphan disease known as Gaucher disease (Type 2 and Type 3). With the help of volunteers and donors we began raising funds with the hope of funding targeted medical research that would begin to pave the way toward a cure.

Limited Research

We knew at the outset that there was little if any research being conducted on the brain as it relates to Neuronopathic Gaucher disease. Our Scientific Advisory Board encouraged us to move forward, assuring us that the medical research community was at the cusp of pursuing this class of brain diseases.

> "To those children whose lives have been curtailed by a caprice of nature, yet whose smiles give us hope for the future."

Research Funded

Although earlier than we had anticipated, we began funding research in 2002 with Dr. Tony Futerman at the Weizmann Institute of Science in Israel. The results of this research were extremely important and were discussed in the September 2005 issue of a major medical journal: Nature Review/Neuroscience. Dr. Futerman asked that we read this article and said, "Note the section on calcium. The CGRF has made a difference".

Medical Conference

In 2004 the CGRF in collaboration with the National Institutes of Health hosted a medical conference in Bethesda, Maryland, that attracted over 100 attendees from six different countries. The most memorable event occurred when one of the researchers said, "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 the world. Thus, the monies spent on one disease may have an even greater impact upon a more prevalent scourge of mankind."

Overlapping Benefits

It was at this point that we realized that this journey is taking us beyond finding a cure for one orphan disease. Researchers are beginning to connect the dots to 26 other lysosomal diseases, Parkinson's disease, and perhaps other brain disorders.

Future Research

We find ourselves today in a position to make a difference far beyond our initial aspirations. It is surprising, and it is exciting. We are financially preparing to fund expensive, but very important long-term research. Sometimes we are amazed at how far the CGRF has come. It begins to make sense when we think about those who have helped along the way.

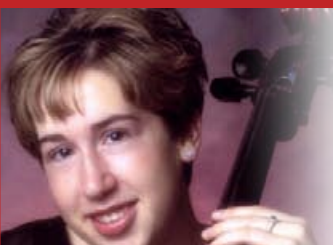
Hope For The Future

Together, this journey will give life to thousands of young children, for generations to come. However, great accomplishments are journeys of great challenge. Along this path there have been lingering doubts that have tempted surrender. But as we look upon the faces of the children, we are re-fueled with passion. Countless individuals have offered their time, their talent, and their hard-earned dollars. You are a collection of compassionate and generous people – people who have joined hands with those little faces to push beyond tragedy, and find a cure.

Deborah Macres R.N.
Founder

Gregory Macres
Chairman/Founder

INSIDE



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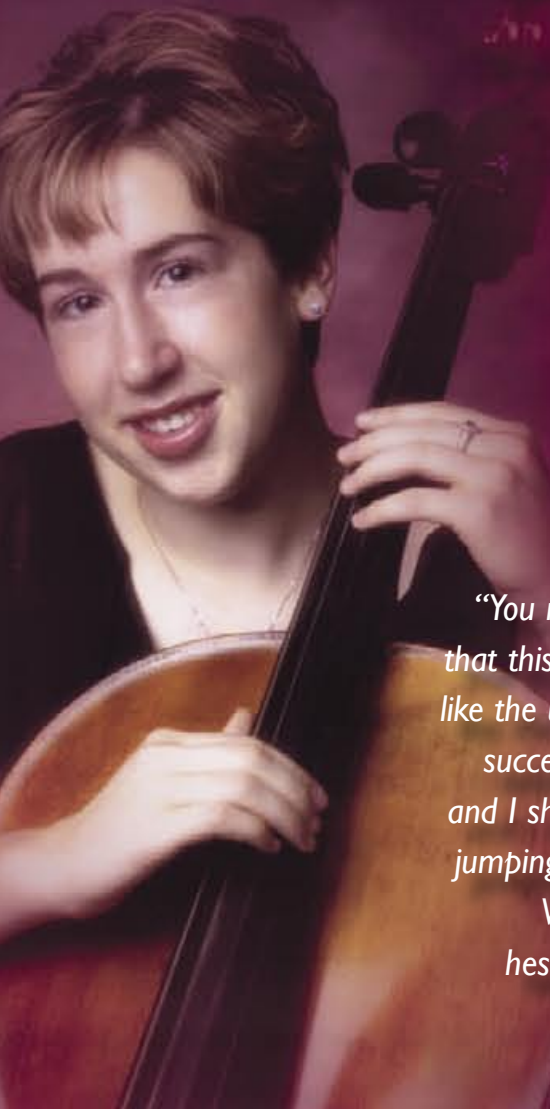

Kristina
Four Years Later

Dear friends;
Much has happened since I wrote the first piece in this newsletter 4 years ago but at the same time I could say that very little has changed. Let me explain this seeming contradiction.

Four years ago Kristina was 14 and just starting high school. She was healthy; indeed you could say she was very healthy. The Cerazyme she took every 2 weeks was doing far more than keeping her alive; she was prospering both physically and mentally. She was a daily runner and maintained a straight "A" average taking the hardest classes possible. In her later years of high school she earned 7 Advanced Placement college credits with perfect scores. She was to become a National Merit Scholarship finalist and had very high scores on the ACT and SAT. She earned an academic scholarship at Colorado College, a small liberal arts school that is often called a "hidden ivy".

"You may say that this sounds like the ultimate success story and I should be jumping for joy. Why the hesitation?"

So now she is 18 and in college. A little homesick but thrilled by the new intellectual challenges. Her Cerazyme is now administered by a visiting nurse in the college health center. These arrangements were facilitated by Genzyme representatives and there was no interruption in the infusion or in insurance coverage. It was a seamless transition.

You may say that this sounds like the ultimate success story and I should be jumping for joy. Why the hesitation? What is the problem?

Don't get me wrong; I appreciate the successes we have to share, and I understand that I could be telling a sad and depressing story like the majority of the stories that have appeared in this column. You see, I feel guilty. Kristina is alive and doing so well and I think of all of the other children who have died from this terrible disease. I think of all of the parents who have a hole in their hearts that will never be healed. Yet these parents continue to

A New Approach to Treatment of

Patients who suffer from Gaucher disease have a genetic defect that results in the insufficient production of an important enzyme – glucocerebrosidase. This enzyme has been reproduced (manufactured) and can be given to these patients intravenously – referred to as enzyme replacement therapy. Enzyme replacement therapy reverses many of the systemic symptoms (in the body) but has little effect on the neurological symptoms (in the brain). Providing effective therapy to the neurological manifestations of lysosomal disease, including neuronopathic Gaucher disease, has been hampered by two obstacles – access and distribution.

Access

The first obstacle is the presence of the blood-brain barrier that prevents the intravenously infused lysosomal enzyme from entering the brain.

Distribution

The second is partial distribution: when one tries to circumvent the barrier by injecting enzyme or genes directly into the brain tissue, the therapeutic agent is not distributed to the entire brain but rather only to a small part of it. This is not very useful in disorders such as neuronopathic Gaucher disease that afflict neurons throughout the brain.

"A potential new approach is the use of small molecules that function as 'chemical chaperones'."

Potential New Approach

A potential new approach is the use of small molecules that function as "chemical chaperones". The most commonly considered these days are molecules that in relatively high concentration are inhibitors of the lysosomal enzyme. They attach themselves to the active site of the enzyme and prevent it from breaking down its substrate, a glycolipid. However, in low concentrations, these chaperones have the opposite effect. They allow the normal folding of the mutated enzyme and the transfer to its normal location in the cell, the lysosome. Once in the lysosome the chemical chaperone is pushed away from the enzyme molecules, allowing them to work better at breaking down the accumulating glycolipid storage material.

Paradox

Initially researchers were simply trying to inhibit (stop) the production of enzyme by using inhibitor drugs. During this process it was found that, at low doses, the drug may actually increase the activity of the enzyme. The paradox lies in the fact that normally, inhibitors knock out the activity of enzymes, but researchers reasoned that at sub-inhibitory levels, inhibitors, by assisting in protein folding, may actually enhance enzyme activity.

Preliminary Studies

Preliminary studies have shown activation of mutated lysosomal enzyme in Fabry disease, Gaucher disease, GM1 gangliosidosis and Tay-Sachs in cultured cells only. Because of their size and their general similarity to molecules of glucose, chemical chaperones can be taken by mouth and may cross the blood-brain barrier to be widely distributed throughout this organ. In order for the chaperones to work, the mutated lysosomal enzyme of the patient has to have some measure of residual activity. For this reason neuronopathic Gaucher disease, which is always associated with some residual enzyme activity, is particularly well suited for this

work for the Children's Gaucher Research Fund. They sell cookies and have golf tournaments and have fund raisers. I feel like I don't do enough; I need to give more. Not just money, but time and effort. In the past four years we have not found either a cure or a treatment for most of the patients with this disease. Babies are still dying and too many parents are grieving. So, we haven't accomplished very much in these past four years, even as Kristina has prospered.

I know you understand the difference between a cure and a treatment. The wonderful drug, Cerazyme that is keeping Kristina healthy is a treatment. A cure would be a procedure that happens once and would mean no further need for treatments. Kristina will be required to have this treatment every two weeks for her entire life. Not just for 5 years or 10 years or until she is 21; the rest of her life. If she stops; she will die, it's that simple. Maybe we will find better ways to administer the drug. Maybe it can be altered to give only once a month. Maybe we will find a way to continuously infuse the drug thru an implantable drug pump like the way some diabetics receive their medication. Maybe it could be injected like a simple flu shot rather than the 3-4 hour infusion process. But, whatever improvements in treatment methods, they are still only treatments and not the ultimate cure. Please understand that I have no problems with the current treatment for Kristina; having the infusion every two weeks is keeping her alive and that's what I want. Do I dare ask for more? Do I anger the gods by hoping for an even better situation? Why can't I just be satisfied?

Why do I want more?

1. First, Cerazyme does not cross the blood-brain barrier. For those of us who can't remember high school chemistry and biology, think of it this way. Try to suck an apple thru a straw. Obviously, the apple is far too large to fit thru the small straw. The size of the molecule used in Cerazyme is too large to cross into the cells in the brain. Because it can't get thru to the brain there is no repair or treatment of the cells in the brain. The lipid accumulates and the Cerazyme cannot clean or purge those cells of the accumulated lipid. In the Type 1 form of the disease there is no problem because the brain cells of these patients do not accumulate the lipid. In the Type 2 form of the disease this accumulation is rapid and causes death within the first two years of life. In the Type 3 form (Kristina's form) the accumulation is slower and children live until adolescence. We don't know why Kristina is 18 and so healthy and smart. Maybe she has a less aggressive genotype than most Type 3 patients. Maybe the 15 years of ERT has some how prevented the lipid accumulation in her body to such an extent that there has an indirect benefit to her brain. Because the drug does not cross the blood brain barrier there is a lingering concern for Kristina. Will the accumulation eventually affect her intellectual or physical abilities?
2. Second, even if Cerazyme provides some indirect benefit for Type 3, it does nothing for Type 2 patients.
3. Third, this is a very expensive drug. Many of us have lifetime limits on coverage. What will Kristina do when she is no longer eligible for our health insurance? Can she secure her own health insurance with her very expensive history?

So, we need to keep working to find both a cure and better treatments. Here is what I know:

- Gene therapy would be a cure but it is still science fiction. Yes, it will eventually come but it is going to take far longer and is far more complicated than Newsweek portrays. It's not as

Lysosomal Diseases of the Brain

therapeutic approach.

Other Diseases Are Also Candidates

However, all lysosomal enzyme deficiencies in which the mutated enzyme is present but does not work properly are candidates for this therapeutic approach. These include patients with Niemann-Pick A, Tay-Sachs disease, forms of neuronal cell lipofuscinosis that are caused by lysosomal enzymes and the mucopolysaccharidoses. The incidence of lysosomal disorders is estimated to be about 1:7000 live births. Therefore, successful application of this therapy would impact Gaucher disease and a number of other "orphan diseases" that collectively are quite common.

Additional Applications (Parkinson Disease)

Chemical chaperones may have additional applications. In recent years evidence has accumulated that even carriers of mutations in the glucocerebrosidase gene (the gene that is mutated in Gaucher disease) are at a higher risk of developing Parkinson disease or other forms of brain disorders that are collectively called parkinsonism. A common pathological abnormality to all these disorders is the presence of cellular abnormalities in many neurons called Lewy bodies. One theory is that Lewy bodies are made of cellular proteins that are misfolded and do not work properly. The misfolded proteins (such as alpha-synuclein) are thought to be toxic to the cell. We are currently testing the hypothesis that the misfolded mutated glucocerebrosidase enzyme contributes to such nerve cell toxicity. This theory may explain why on rare occasions and in susceptible individuals the presence of mutated glucocerebrosidase causes dysfunction and death of neurons that leads to Parkinson's disease or parkinsonism disorders. If this hypothesis is correct, chemical chaperones, because of their ability to favor correct folding of the mutated enzyme, may help lower the risk or slow the progression of patients with Lewy bodies-related disorders who also have at least one copy of the mutated glucocerebrosidase (Gaucher) gene.

> "Therefore, successful application of this therapy would impact Gaucher disease and a number of other "orphan diseases" that collectively are quite common."

Potentially Quite Safe

When engaged in medical research one must always consider the potential risks (side effects) of any therapy that is being pursued. This is true with current potential therapies such as Intrathecal Infusion of enzyme into the brain, Bone Marrow Transplantation, Gene Replacement therapy, Neural Stem Cell Therapy and Substrate Reduction therapy. One significant benefit to chemical chaperones is that they are expected to have a rather specific action and therefore be quite safe and much less invasive than more remote approaches mentioned above. As these compounds have been developed through animal studies and on to human studies, of importance has been the remarkable lack of any serious toxicity. In addition, because they are small molecules of the size of a glucose, they should go to every organ in the body including the brain. However, it is always

simple as isolating a single missing or defective gene and transferring a good gene into the cell. Even when they find a delivery system it may take years to design gene therapy for each of the individual diseases and maybe more for the individual variations. This is going to be an enormously expensive situation.

- There are several efforts to finding better treatments. For example:
  - They are trying to place the enzyme directly into the brain as a way to bypass the blood brain barrier.
  - You have heard about the trials sponsored by NIH involving Zavesca which is a drug taken in capsule form that may actually cross the blood brain barrier. Kristina was on that protocol for a year and it was not a pleasant experience. Maybe they can eliminate the side effects and show better results affecting the neurological system.
  - There is a new treatment being researched which chemically refolds the misfolded proteins involved in the disease and having something called chaperones that carry the missing enzyme across the blood brain barrier.

All of this research takes money. Who is going to fund the research for a rare disease where many of the patients die within the first years of life and that affects fewer than 1,000 living patients worldwide?

Who is going to speak for the children?

Hopefully, the answer to that question is you. We will try to help you as we try to identify the specific research that needs to be funded and will not duplicate the efforts being made at the NIH or by private companies.

That's why I say that nothing has changed in the past four years and that's depressing. The work has just begun.

possible that significant negative side effects will be revealed when given to patients in clinical trial.

Clinical Trials

We expect that clinical trials with suitable oral agents will take place in the coming months and years for the treatment of neuronopathic Gaucher disease, other lysosomal diseases of the brain and possibly also for patients with Parkinson disease and glucocerebrosidase (Gaucher) gene mutations. Although there are many potential roads to travel in our quest for a cure, chemical chaperones is one road that should, and will be pursued.

Raphael Schiffmann M.D.
Lead Investigator
Developmental and Metabolic Neurology Branch
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2005 Charity Golf Tournament's

Sacramento

June 20, 2005 marked the Fourth Annual Coldwell Banker 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.

San Jose

The 9th Annual Gregory Austin Macres Memorial Golf Tournament to benefit the Children's Gaucher Research Fund was held on September 29, 2005, at Cinnabar Hills Golf Club in San Jose, California. Sponsored by Coldwell Banker Silicon Valley, the full-field shotgun tournament was enjoyed by over 200 golfers. We thank the tee sponsors that included local title, mortgage and pest control companies. After 18 holes of golf, the golfers enjoyed a cocktail hour, a silent auction, dinner, and raffle awards.

Over $80,000 Raised For Medical Research

We extend our gratitude to the members of the golf tournament committee's and the many volunteers in both San Jose and Sacramento who year after year pour their heart and soul into these extraordinary events.

John Carman's Bike Brigade

No one asked John, he just decided to do it. Three years ago John Carman started the "Bike Brigade" and rode 45 miles to the Gregory Austin Macres Memorial Golf Tournament. Others have joined him raising thousands of dollars for medical research. We asked John why he does it:

"We have an obligation. It would be disrespectful toward the gifts and blessings that have been bestowed upon us if we do not give back to the world. Thank you for allowing me to share. God bless!"

Vlade & Ana Divac ~ *"A Diamond In The Rough"*

In our last newsletter we introduced Vlade and Ana Divac and shared with you their desire to help "raise funds for a cure" during our 2005 Summer Fund Raising events. The Divac's graciously offered the use of their restaurant, L'Image, an upscale establishment located in the Pavilion shopping center in Sacramento. Vlade and Ana participated as our "celebrity guests" at a private dinner and a celebration party held this past July.

Private Dinner

Our fourteen guests gathered the evening of July 21st anxiously awaiting the arrival of Vlade and Ana. I had the pleasure of working with Ana in the months leading up to these events and found her heart of compassion to be just as it had been described in the local newspapers. This evening however, I would meet Vlade Divac (the NBA Basketball legend) for the first time. For years my wife had suggested that I avoid standing (for extended periods) next to those who exceed 6'4". Tonight, I was the host, required to stand next to Vlade (7'1") and do my best to make everyone feel comfortable – including myself. I greeted Vlade for the first time with a handshake, and in an effort to break the ice I explained to him that my basketball career had been cut short at birth. Vlade took the cue and it was soon clear to everyone in the room that they could relax – Vlade's sense of humor and down-to earth spirit put everyone at ease.

Celebration Party

Naturally, we all wonder what it would be like to be a celebrity. Would we let it go to our head? Would we eventually become irritated by the attention? Would we develop an aloof air of superiority? The autographs – the photo's – crowds gathering around as though you were a King. On this warm Sacramento evening there were over 250 supporters of the CGRF waiting for the King - The NBA Sacramento King who is so revered by the community. There were no limits on photographs – there were no limits on autographs – and there was no limit to their humble nature. One guest that evening spoke for all 250 guests when he said, "I have read all the articles about Ana and Vlade. All of them say they are genuine, real people who help with so many charities. It has always been said that they really do care. When you meet them is person you feel their sincerity – It renews your faith in people. They are a diamond in the rough."

"You would think that she had lost a child to Gaucher disease. Anna speaks from her heart and captures the crowd."

In Loving Memory of
Selena Marie Rodriquez

"Our Little Pupa"
May 31, 2004 to May 13, 2005
Hamilton, Ontario
Canada

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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