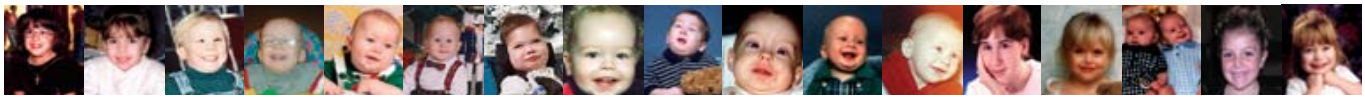
Winter 2007-2008

HELPING HANDS

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



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THE ONLY THING INCURABLE IS OUR PASSION

Nerve cells gone bad – a developing story

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Scientific research is fascinating

Just think where we were a few years ago in terms of understanding what is going on in neuronopathic Gaucher disease. Basically, we knew nothing. Yes, we knew that these unfortunate children were sick with some kind of neurological disease, and we knew, sadly, that there was little hope for them. Today, thanks in part to the great efforts of folks who have supported the Children's Gaucher Research Fund, we know much more. We know a little about the mechanism by which nerve cells start to dysfunction (that is the calcium story – more of that later). We know a little more about some of the specific nerve cell types that are affected in this disease. And although not directly supported by the Children's Gaucher Research Fund, recent work by a laboratory in Sweden has produced the first mouse model of neuronopathic Gaucher disease, and the results of the initial studies using this mouse confirm the work of my laboratory suggesting that nerve cells are the primary cell type affected in the disease. So, much progress has been made over the past 7-8 years. That is not to say that we can stop now and rest on our laurels – absolutely not – but we can certainly be pleased with progress made.

Serendipitous experiment

For those of you new to this field, or reading this newsletter for the first time, let me fill you in with a little background. I am a basic scientist, not a physician, who got into the field of Gaucher disease at the end of 1998 by a serendipitous experiment which led us to suggest that calcium physiology might be altered in nerve cells of Gaucher patients. At this point, we were made aware of the Children's Gaucher Research Fund, and received our first grant to support this work. At the end of the first funding period we had made significant advances in understanding the relationship between the lipid that accumulates in Gaucher disease (the lipid is known as glucosylceramide) and defective calcium physiology, and had shown that our hypothesis was also valid for human patients. The latter observation was particularly satisfying as we were able to show a direct link between the amount of glucosylceramide that accumulated in human brain and the severity of neurological disease – this meant that our previous work, all done in animal models, could indeed be validated in human tissues. Of equal excitement were the observations, by our laboratory and also another laboratory, that defective calcium physiology might account for the pathology in some other, similar diseases, such as Sandhoff disease (a form of Tay Sachs disease), Niemann-Pick A disease, and the GM1 gangliosidosis. It is perhaps not surprising that defective calcium physiology plays a role in these diseases as calcium is a key player in many processes that occur in nerve cells, but it was nonetheless of huge significance to discover an underlying role of calcium.

> "… this meant that our previous work, all done in animal models, could indeed be validated in human tissues"

So what's next?

We had shown a role for calcium, had received funding from the Children's Gaucher Research Fund, and were happy in general with our progress, but still wanted to know more. How could we proceed? Before I continue with this, let me say that the reality is that very few researchers have focused to date on attempting to understand the underlying mechanisms in neuronopathic Gaucher disease. This is because the disease is rare, little funding has been available, and there have been no suitable animal models. I believe that the low level of interest from the research community is about to change, and again, this is in large part due to the efforts of the Children's Gaucher Research Fund. One way in which this has come about is the bi-annual conference on Lysosomal Diseases and the Brain, sponsored by the Children's Gaucher Research Fund, the fourth of which will take place in May 2008 in Sacramento. This conference brings together basic and clinical scientists from different backgrounds to discuss the biochemistry, cell biology, and neurobiology

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At the moment, there are 3 people working on Children's Gaucher in my laboratory, two graduate students (Tamar Farfel-Becker, on the left, and Einat Vitner, on the right) – I am shown in the middle. Due to the new CGRF grant, we are about to employ a fourth person, a research technician who will allow us to push forward the research

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of these diseases. For instance, at the 2008 conference, there will be a lengthy discussion on the cell biology of glucosylceramide. That is a bit esoteric, I can hear some of you saying. But no, it is not. Remember, that Gaucher disease is caused by accumulation of glucosylceramide in cells of the body, and in nerve cells in the case of neuronopathic Gaucher disease. So understanding

"Due to the funding of the Children's Gaucher Research Fund we are able to increase our research team."

what it does in normal cells is essential if we want to understand what it does in Gaucher cells. There will also be a discussion on lysosomes, the part of the cell in which glucosylceramide is believed to accumulate. Thus, one of the goals of the conference is to attract new researchers to this field who may have a unique (and hopefully correct!) insight into what might be going on in this disease.

Let us go back to 2005

To return to the research that my laboratory is doing, let us go back to 2005. As I said earlier, we had shown a role for defective calcium physiology in Gaucher nerve cells. What was next? Well, what is the precise mechanism by which calcium levels are altered? What are the biochemical signals that induce these changes in calcium levels? What are the biochemical events that occur after the changes in calcium levels? Is the genetic program of the cells altered in such a way that would give us a clue about the pathways that are turned on or off which eventually cause nerve cells to die? Are other cells in the nervous system, in addition to nerve cells, also affected? If so, what is the relationship between all these events that may be taking place in different cells?

Are these questions actually important? Wouldn't it simply be better to focus on developing a therapy for the disease? Making a therapy is of course the ultimate goal, but I believe that the real breakthroughs in development of therapies will only come after we understand more about what is going on in the disease at the basic science level. For instance, if we understood the biochemical pathways that are affected in the disease, maybe we could slow disease progression by using available drugs that are known to interfere with these pathways. If we understand the biochemical pathways, then maybe we could even make new drugs to help alleviate symptoms.

Research Funded

"I believe that the low level of interest from the research community is about to change … this is in large part due to the efforts of the Children's Gaucher Research Fund."

In this regard, I am of course preaching to the converted since the philosophy of the Children's Gaucher Research Fund has indeed been to support basic science, and I was therefore delighted to receive news recently that the Children's Gaucher Research Fund has generously agreed to support our work for another three years. This time we will focus on the issues discussed above to further our understanding of the precise biochemical and genetic pathways involved. Due to the funding of the Children's Gaucher Research Fund we are able to increase our research team to 4 people, and to double our efforts to understand more about the defective underlying biochemistry. Moreover, we are about to initiate a collaboration with a group in Sweden who have recently made the first mouse model of neuronpathic Gaucher disease. This research team, lead by Dr. Stefan Karlsson, has made a mouse which mimics many of the symptoms of the disease -- time will tell how good a model it is or whether additional models are also needed – but availability of this mouse is a huge step in research into Gaucher disease and the brain. Gratifyingly for us, Dr. Karlsson suggests that the major cause for brain defects in these mice is because of defective nerve cells, rather than defects in other cells which then cause, as result, a defect in nerve cell function – this is entirely consistent with our findings over the past few years.

Scientific research is indeed fascinating, and progress in understanding what is going on in Gaucher disease is, I believe, about to pick up pace. And none of this would have been possible without the commitment of the Children's Gaucher Research Fund, and of course donors to the Children's Gaucher Research Fund, towards basic scientific research. Breakthroughs may be around the corner, though this can never be guaranteed in scientific research. But one thing is for sure – there are no breakthroughs without funding to do the research, and this is where the Children's Gaucher Research Fund has played, and will continue to play, such a vital role.

Let us introduce ourselves: we are Rick (dad) and Gloria (mom) Loncharich. We would like to tell you about our daughter, Danielle.

danielle loncharich

Tuesday September 9, 2003 was a day that changed our lives forever; one that was like no others before. It was to be a routine day, like the many pediatrician visits with our four children: Alexa, Blake, Jace and Danielle. On this day, our youngest daughter, Danielle, had her 18-month well-check visit.

During the examination, our pediatrician Dr. Somes, detected a potential problem with Danielle. She said she did not want to alarm us, but already had called the radiology department at St. Vincent Hospital and ordered an emergency ultrasound and blood testing for Danielle. Danielle never pulled away as Rick clenched her with a wrestling hold and a needle entered her arm to extract her blood. She only whispered "ouch" in her small comforting voice. Later that evening, the pediatrician called us and indicated Danielle had an iron deficiency and her spleen was enlarged. Her first concern was that Danielle had a tumor, so we were relieved that none was found. Now we had to figure out why her spleen was enlarged.

Dr Somes had already called Dr Hock, a pediatric hematologist at the Center for Cancer and Blood Diseases at St. Vincent Children's Hospital for additional blood testing. Dr Hock reviewed the previous day's ultrasound and lab results and also viewed her blood under the microscope. He didn't think the problem was leukemia. The sigh of relief was overwhelming. He did, however indicate her red blood cells were fewer, lighter in color and smaller than normal. He ordered more than 20 tests requiring another 10 vials of blood be drawn from Danielle. The doctor indicated we should also be careful with Danielle as her spleen is so enlarged that it is no longer protected by her rib cage. Over the next few weeks test results were negative for a number of diseases; it was speculated that maybe a virus caused her enlarged spleen.

On Wednesday October 22, it was discovered that her spleen appeared to dramatically increase in size. Shockingly, the doctor indicated he wanted to perform an immediate bone marrow test. Despite the significance of this test, we were still optimistic he wouldn't find a serious problem. We watched Danielle from the time she was born on January 21, 2002. She had always been full of energy and life. No matter how the day was, upon hearing the door open she would run to the door with an electrifying sparkle yelling "Daddy", or "Mommy" and wrap her arms around you as she was whisked into the air for a big kiss and hug. As every parent knows, this is what makes life and parenthood worthwhile. Everyday problems and issues seem to disappear with the love of your life in your arms. The warmth, satisfaction, and knowledge that you brought this special child into the world radiate with each embrace. Mere words can't describe the immense joy.

During the bone marrow test they also extracted some cells for a biopsy as well. He found cells that were a different shape – like that of crinkled up paper, and suggested a rare disease called Gaucher disease. The doctor had never seen this disease before. However, it just so happened that the pathologist had recently returned from a seminar that discussed Gaucher disease, which is why he recognized the appearance of the cells. This "coincidence" was one of many times that we felt the hand of God during this process. The doctor recommended we send a sample of her blood to the Mayo Clinic for specific enzyme testing. Our stomachs were unsettled and our nerves jittery as we waited for

the results. Drs Somes and Hock recommended we schedule Danielle for an appointment at the Cincinnati Children's Research Hospital on November 12, as a leading expert on the disease practices there. We lacked the enzyme results, but reasoned she should be seen by an expert; someone who actually had seen patients with the disease. Surely they could confirm our hope and prayers that she did not have this disease.

As the day arrived, we spent the afternoon with Dr Grabowski and his geneticists. The geneticists asked questions and took our family history. Blood samples were again taken, but with these samples Dr Grabowski wanted to analyze Danielle's DNA and look for mutations that would definitively confirm the disease. Danielle spent the three hours in the office, much like any other child, climbing up and down on chairs, reading her books, and whimsically chattering. Danielle had always been advanced in speech. She spoke her first words at age 6 months bellowing out "Ma-ma" and "bug". We knew that Danielle would be special in life. She was a true gift from God and had a magnetism that would attract anyone and light up their lives with her captivating grin and charismatic charm. .

The next day we finally heard back from the Mayo Clinic. Unfortunately, the moment we dreaded hit us – her test showed a very low level of enzyme and low white blood cell count consistent with the disease. The Cincinnati Children's Research Hospital also found two mutations in her genetic code unequivocally confirming the disease. Neither of us could speak. We had difficulty swallowing and breathing became difficult, a tremendous weight fell upon us. We were not looking for pity, but answers to the age-old question of why? Why her? Why Danielle? Why did this have to happen to her, to any child? You begin to question so many things. Perhaps, the most important message that Dr Grabowski left us with is fitting here, "It doesn't matter what type she has, we will take the disease on as it comes." And this is truly the path that we take. She is doing very well, but we hold our breath every time he looks at her eyes – checking for those neurologic indicators of involvement.

Dr Grabowski suggested we take Danielle to the Riley Children's Hospital in Indianapolis where Dr Wappner would oversee her treatments. At the first visit she took measurements of her body, watched the way she walked, and performed tests for eye and hand coordination to document a baseline of the disease. Her spleen was 20 times normal size and her liver was twice normal size. Her spleen was so large it extended down into her pelvic region as far as it could go. She looked like she was 9-months pregnant despite being a little girl of 18-months in age. She is a beautiful girl, frequently complimented by others. She has an ornery grin that can captivate everyone. Strangers often comment on her big beautiful brown eyes with the natural Maybelline eyelashes.

The doctors have labeled Danielle as type 1 or type 3 Gaucher disease as her specific gene mutations are both severe. Some DNA mutations are predictive for the course and progression of the disease. However, with DNA mutations consistent with Danielle's there has been a Japanese report of several patients that exhibited all three types of the disease. In other words, the mutations alone cannot dictate the form (type 1, 2 or 3) of Gaucher disease. Only time and symptoms will provide clues to an accurate classification for Danielle. Enzyme replacement therapy can alter the course of the disease compared to patients that had the disease prior to discovery of this treatment. (But the same impact has not been observed with the neurologic forms.)

Danielle had surgery on December 2, 2003 to install a port-a-cath so she will not have to have an IV needle stuck in her little arms and veins with every infusion. The port is centered on her breast bone, is about the size of a nickel and a half inch protrusion above her chest. Two days after surgery we went to have her first infusion therapy and CT scans so they can monitor the size of her spleen and liver as treatment progresses. Infusions are now done at home. For quite some time now, we have had the same nurse for the infusions and Danielle looks forward to "Nurse Wanda's" visits. They've developed a special relationship.

It's been an intense roller coaster ride. Rick is a scientist, working at Eli Lilly Pharmaceuticals. He's a thinker, a studier. He jumped into studying Gaucher disease with both feet. He reads the research papers and talks to the researcher and doctors about possibilities. He contacted a previous boss at the National Institutes of Health and got one of his post doctoral candidates working on studying Gaucher disease. Gloria personally believes that Rick has a bigger purpose and greater possibility to positively impact the disease. Gloria is the mom all the way. All emotion. Some denial. It took some time to come to terms with our situation and accept it. Pouring out the maximum amount of love and focusing our support group has been the mainstay. Our prayer team is huge and has played a major role in our lives and her success. We cling to our faith like a life raft and thank the Lord for the blessings He pours out on a continuous basis. As we walk the tightrope between type 1 and type 3, God is our safety net all the way.

In spite of her situation, Danielle continues to be a very happy, energetic, enthusiastic and beautiful girl. She's as smart as a whip and quite a character. She's resilient, head-strong and independent. She simply lacks a necessary and vital enzyme in her body. She is one of our most precious gifts. She has taught us so much. She has re-focused us on our true priorities. We knew she was special from before the time that she was born. She showed us spunk in utero and tested our limits during the pregnancy. She was our only one that required an amniocentesis (which caused us a week of fear, followed by one phone call of sheer joy). She was the only one who introduced us to the concept of having Strep B during pregnancy, but this also turned out fine with the proper follow up. We hoped that the Gaucher test would turn out similar – another false alarm to keep Mom & Dad on their toes. She lights up our lives with every moment, with every gaze of her big brown eyes, with every touch, every kiss and with every soft embrace. She is a precious gift, a gift from above, a gift beyond any others, a gift of un-ending giving, of unconditional love. She is ours, our flesh and blood, our life, our life worth living.

One thing that really bothers us is that this disease is unlike that of diabetes, cancer, muscular dystrophy and many others, in that it is not well funded nor well known. It is our dream that we can help make a difference.

Rick and Gloria Loncharich
Carmel, Indiana

A Miracle in the Making

EVERY FALL, I GET TO WITNESS A MIRACLE IN THE MAKING.

For the past five years, I have had the great fortune of being part of the Golf Tournament Committee for Coldwell Banker Northern California which sponsors the annual Gregory Austin Macres Memorial Golf Tournament to raise funds for the Children's Gaucher Research Fund. As the committee co-chair the past three years, I have been able to witness first-hand the amazing heart and altruistic spirit that is the Coldwell Banker Northern California family.

This year's golf tournament – the 11th annual event – was held on October 4 at Cinnabar Hills Golf Club in San Jose and was appropriately dubbed "Give a Child a Mulligan" (for those not familiar with the golf term, a mulligan is a "do over"). More than 150 members of the Coldwell Banker Northern California family – from as far north as Sacramento all the way down to Carmel and everywhere in between – joined us for the special fundraising event.

Personally, I can tell you that there is nothing more rewarding than being there the day of the tournament and seeing our committee's countless hours of hard work (which began twelve months prior), planning and detail come together so beautifully. One of the event highlights is when Greg Macres gives his update as to the progress and advancements that been made in finding a cure for the disease – and how the fundraising monies from our golf tournament go towards that fight; it is something which always brings me and others to tears. It is truly inspiring and heartwarming to know that our hard work, along with the support of so many individuals, is making such an impact.

Through this year's golf tournament and accompanying silent auction and raffle (we had more than 40 items!), we raised approximately $22,000 for the Children's Gaucher Research Fund…every dollar of which brings us one step closer to finding a cure for these children.

There are countless individuals who were instrumental in making this day a success for the Children's Gaucher Research Fund. They include members of our Coldwell Banker Northern California Marketing Department and Golf Tournament Committee – Heidi Bonnel, Matt Geiser, Melissa Huntsman, Jenna Oliphant and Anne Treacy; our wonderful sponsors who year after year turn out to support the cause; countless volunteers from our Coldwell Banker Northern California Support Center and local offices; and last but certainly not least, Silicon Valley-Monterey Bay President Joe Brown who worked tirelessly to promote the event and ensure its success.

I know that I speak for everyone involved in the event by saying that the long day of "work" is totally worth it just knowing we have helped make a difference.

By establishing the Children's Gaucher Research Fund, Greg and his wife, Deborah, opened the gateway to a new world in which children get another chance at life. As each year passes, we get steps closer to that reality. What a miracle it will be to see.

50 Year Anniversary – Our Idea Was a Tremendous Success

"We are Ron and Ada Schirf from Latrobe, Pennsylvania. Our youngest grandchild Danielle was diagnosed with Gaucher disease in November, 2003. This past August was our 50th Wedding Anniversary. We wanted to celebrate this event with our family and friends but at this point in our lives we don't 'need any more stuff'. We decided to use this opportunity to channel the generosity of our friends and relatives to the cause we are most passionate about. From the very beginning almost everyone we know has been kept informed of Danielle's medical condition. We felt this was a great way to enjoy our anniversary party with donations going to Gaucher disease research. Our idea was a tremendous success."

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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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P.O. Box 2123
Granite Bay, California 95746-2123

2008 Conference: Lysosomal Diseases and the Brain

The next Lysosomal Diseases and the Brain conference is scheduled for May 29-31, 2008.

POSTER BOARDS WELCOME!

Details can be obtained by visiting www.lysosomal-brain-conf.org.

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