The Children's
Medical Research
Foundation, Inc.®

KirbyGram

The latest news on Kirby Wilson and friends and the search for a cure for Sanfilippo Syndrome

June 2003

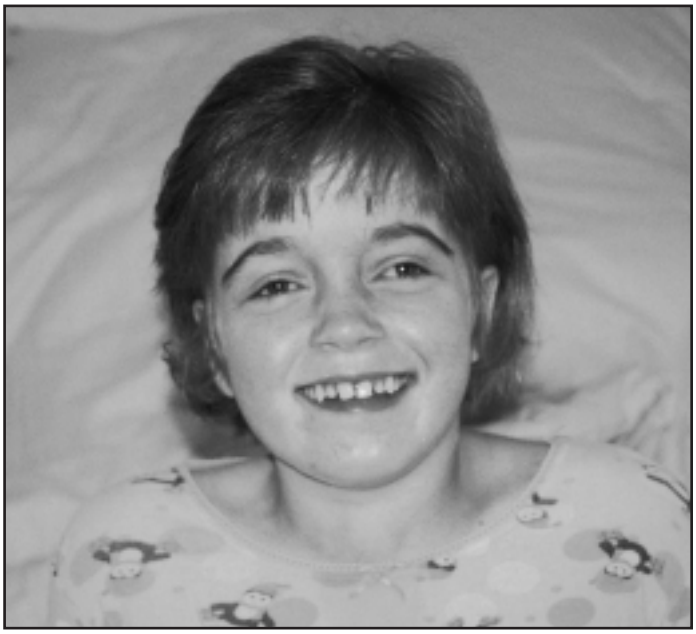
What is Sanfilippo Syndrome?

Sanfilippo Syndrome is one of seven Mucopolysaccharide (MPS) disorders. There are four different enzyme deficiencies that cause Sanfilippo. The Sanfilippo disorders are described as type A, B, C, or D. There is very little difference between the four types, though there have been a few very mild cases of the B form reported where the children have remained relatively healthy into early adult life.

Children with Sanfilippo are missing an essential enzyme that breaks down a complex body sugar called heparan sulfate. This sugar slowly builds in the brain, stopping normal development and causing hyperactivity, sleep disorders, loss of speech, mental retardation, dementia and finally death by age 10-15 years. There is no cure yet.

While Sanfilippo occurs once in 24,000 births, successful research into the disease could apply directly to many of 5,000 other genetic disorders.

KIRBY UPDATE



Kirby smiles for the camera

In March Kirby was all smiles as soon as her feet hit the beach in Florida, where the Wilsons spend their spring vacations. Long walks at the water's edge, floating in waves and "hut hopping" with friends for "smoothies" were her favorite activities, when not relaxing in her own beach chair, simply watching the world go by.

"These spring vacations have always been a wonderful break for our family," Sue Wilson explains, "as we have always found them to be not only a time for relaxation for each of us, but most importantly, rejuvenation as a family. The real bonus for Brad and me this year was to see how Kirby continues to remember and truly enjoy her time at the beach."

April 15th marked Kirby's 12th birthday, which was celebrated with the ever favorite, pizza, Coke and cake. There were no smiles to be had at the dinner table, as Kirby took the consumption of her dinner, a special treat, very seriously. It was only after she had had her fill that she acknowledged her loving family with smiles and happy vocalizations. "It is a blessing to see Kirby recognize and enjoy favorite meals with that smile of hers that warms our hearts and inspires us to continue with a very special mission," Sue comments.

"We are also extremely thankful to report that Kirby's days at LaGrange Highlands Elementary School continue to be filled with kindness, says Sue." "A note came home this year telling us that so many 5th-grade peers had signed up to do activities with her that they had to make room on her schedule for this activity two times per week. The children of Highlands amaze us time and time again with their compassion, which continues to remind us that 'One cannot be grateful and unhappy at the same time.' Brad and I are grateful for the staff and children who surround her each day."

FUNDRAISING NEWS

"Sweethearts" Set A Record

"Sweethearts" Robert and Alison Credit with Brad and Sue Wilson

The Eighth Annual Sweetheart Dinner Dance, held February 7th, was attended by 250 "sweethearts," who helped set a profit record of more than $104,000! This year, a special touch was added to the event by The Drake Hotel, with an all-employee fundraiser of its own, "Red Day," where employees wore red to signify their support of the Foundation. Sue Wilson states, "I have always said this evening is a special one for Brad and me and serves as a wonderful beginning to each year, but it just gets better and better! The enduring commitment of our guests toward Kirby and others like her, and now, this year, seeing the employees of The Drake, everywhere we looked, dressed in red for our little girl, leave a special mark in our hearts that will not be forgotten." Sue adds, "Words cannot express our gratitude toward all the people who contributed to make this dance extraordinary in so many ways."

The Foundation Gives Thanks…

To our dear friends at **Highlands Presbyterian Church** for their continued love and support of our family and Foundation.

To the **Junior Girl Scouts of Troop 765**, Kirby's fifth-grade buddies, for their donation from the troop's annual cookie sale to "help find a cure" for their classmate. Too sweet!

To **Rick Goldwasser** and **Barry King** of **SCORE Sports Venture** for their many donations and tennis fundraisers. Game, set and match for Kirby!

To **White Hen Pantry**, **Kirschbaum's Bakery** and **Casey's Market**, all from Kirby's hometown of Western Springs, for their continuous fundraising efforts using cash jars. And to the people of the community who fill them, your "hometown girl" thanks you from the bottom of her little heart.

To cousin **Molly Russell** for always thinking of Kirby and throwing a big bash to raise some cash! And, we can't forget all the friends who came to the bash with the cash! Kirby loves a good party!

And To The Families Working Together For The Cure

Mr. & Mrs. Lyle Everson and **Waste Management of Colorado, Inc.** for their most generous support in honor of **Douglas** and **Cameron Nicoll** of Colorado Springs, CO.

Kirby with Cousin Molly

FUNDRAISING NEWS

Super heroes Robert and Sean Smith

Kathy Smith of Freehold, NJ, for her donation in honor of her children, **Robert** and **Sean**, and the staff of **Leggetts Sand Bar**, who helped to make this donation possible.

Greg and **Toni Graham** of Salinas, CA, parents of **Jacqueline**, for their continuous fundraising efforts with their foundation, **Little Jacq's Corner**, to benefit The Children's Medical Research Foundation and its mission.

Anna Kidwell, of Lexington, KY, mother of **Ashleigh** and **Brooke**, for her solicitations on behalf of the Foundation and most generous support of the Sweetheart Dinner Dance's silent auction.

Brad and Sue are grateful for your help on behalf of some pretty special children.

News From Connecticut

The Logan's family friend, **Linda Casorio**, is hard at work putting the finishing touches on the annual "Cut Against Time" fundraiser to be held June 8th. The Logans are thrilled that the event will take place this year. For the sixth time, many of the hairdressers who participated in the first cut-a-thon will return in support of Rhianna. Rhianna will attend the "Cut Against Time" event, which becomes even more of a reality to all those involved, for she is now10-1/2 years old. Spirits are high for a successful event.

Rhianna's one-to-one aide at school, Sandy Crowe, took the opportunity to support the Logan's fundraising efforts by writing to family members and business friends. Speaking of her personal connection with and the beauty of Rhianna, she was able to add $900 to the total raised at the "Rockin' for Rhianna" dance, which was held last October. Another wonderful result of her efforts was the most generous donation to the Foundation from the Pelletier Family Foundation.

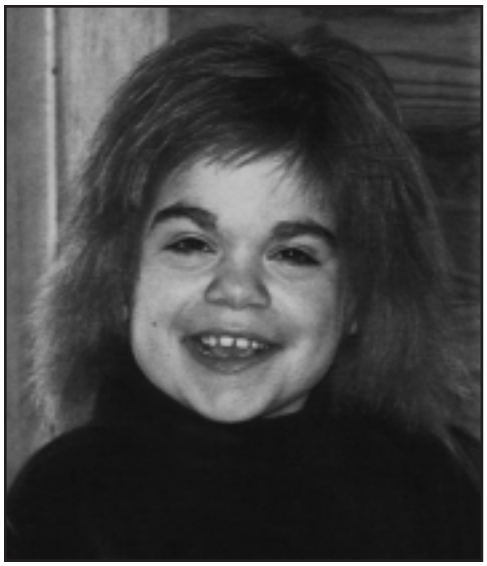
The Logans and the Foundation also extend their most sincere thanks:

To the members of the **Connecticut Area Classic Thunderbird Club** for choosing the Foundation as one of the benefactors of the proceeds of the club's annual "Time Machine" Car Show.

To **Martha Couture** of **An Artisan's Marketplace** for helping "Rhianna's Hope" with her annual "Santa for Hope" raffle.

To **Mary Lou Cassille** of **Cassille's Restaurant** and its customers for their continued support of Rhianna with "cash jar" donations, and

To **Cory** and **Donna Gabel**, Rhianna's aunt and uncle, for their ongoing donations of a portion of the proceeds from Cory's solo piano instrumental CD, "One Road," to the Foundation. Sales continue, as do donations to the Foundation. Interested in this new "spin" to help? Just contact the Foundation to obtain a copy or log on to Cory's website at cdonavan.com.



Rhianna is all smiles

NATIONAL MPS SOCIETY UPDATE

Linda Shine retired at the end of this past year after four years as President of the National MPS Society. Linda was instrumental in initiating significant changes and growth in the Society. This group now strives to provide support for families of all MPS disorders, create public awareness, and, through its Legislative Committee, advocate changes in federal laws that will benefit MPS children's quality of life and education within the public schools, as well as promote federal funding of MPS specific research. The Society, which has grown over recent years to 700 members, will issue eight grants this year, totaling $470,000, to researchers with a common goal of eradicating all MPS disorders.

Linda Shine (right) with Executive Director Barbara Wedehase, who shared her vision

"I am sure Brad and I are joined by many others when we express our utmost respect and gratitude to our dear friend for sharing her vision of what the Society could be, her drive and talent to change it, and for a job extraordinarily well done," summarizes Sue.

RESEARCH UPDATE

University of North Carolina - Chapel Hill April, 2003

The long-term goal of our research is to treat central nervous system (CNS) diseases in MPS IIIB patients, using adeno-associated viral gene therapy.

With the support of The Children's Medical Research Foundation, we have made AAV vectors (means of carrying genes into cells) containing the normal human α-N-acetylglucosaminidase (NaGlu) gene, which is missing in MPS IIIB patients. We have previously shown that our AAV vectors mediated the production of NaGlu (the enzyme missing in MPS IIIB) and corrected the storage of glycosaminoglycan (GAG, previously called mucopolysaccharides) in cultured human and mouse MPS IIIB cells. Using AAV vectors, injected into mouse brain, we have also demonstrated the long-term, but only localized production of the missing enzyme and the localized correction of lysosomal storage in MPS IIIB mouse brain in the area of our injection. In addition, we have observed the correction of GAG storage in liver (50-80%) and in other peripheral tissues (<40%) of mice, by a single intravenous (I.V.) infusion of the AAV vector.

The critical issue in developing treatment for the CNS diseases in MPS is to be able to deliver therapeutic reagents (AAV vector) to the whole brain and not just a localized area. Enzymes and vectors, when given by an I.V. injection, are prevented from entering the brain, due to the presence of a physical barrier called blood-brain barrier (BBB). We have been recently focusing our research efforts on developing methods to enhance vector delivery to the brain. 1). We have successfully delivered the AAV vector into CNS by a single I.V. injection, using mannitol to disrupt the BBB. Simultaneously we achieved a global distribution of the

vector in the brain of mice, even though the number of brain cells involved was still small. I.V. administration could also deliver AAV vector into multiple somatic tissues. More efforts are needed to increase the efficiency of the process. 2). We injected AAV vector into a spinal fluid space (cistern) in adult mouse brain and achieved broad dispersion of the AAV vector in the CNS, including brain and spinal cord. Both approaches above are less invasive compared with direct injection into brain tissue. We anticipate that combining the peripheral (I.V) and intracisternal delivery of AAV vector will contribute greatly in developing therapies to treat physical and neurological diseases in MPS. This may also benefit therapeutic studies for other lysosomal diseases since they share many similar features. More studies are needed to explore more efficient means for delivery of AAV vectors to the whole brain, in order to pursue our goal of treating CNS disorder in MPS IIIB patients. Dr. Haiyan Fu has done the studies in the laboratory of Dr. Joseph Muenzer at University of North Carolina at Chapel Hill.

University of South Florida April, 2003

In the last few years, our research group, led by Dr. Paul R. Sanberg, University of South Florida, has studied the potential of human umbilical cord blood stem cells to treat various neurodegenerative disorders. Data suggest that these cells are able to differentiate into pre-neural cells, making repair of an injured or defective nervous system possible.

We intend to continue our study using cord blood cells in a mouse model of Sanfilippo type III B for cell therapy by delivery of the deficient *Naglu* enzyme; this missing enzyme leads to heparan sulfate accumulation. In preparing the groundwork for this purpose, we tested cultured cord blood cells for *Naglu* enzyme. We found evidence that these cells contained the *Naglu* enzyme and released it into the culture media. Finding the enzyme outside the cells was an important step, suggesting that *Naglu* enzyme from transplanted cells would be available to reduce heparan sulfate accumulation (a consequence of *Naglu* deficiency).

All animals used in the study were obtained from our established colony of *Naglu* mice. Forty-five mice (1 mo. of age) were used; most mutant mice received transplants with either hUCB cells or a similar volume of inert media into the brain while the remaining mice served as controls. Mice were tested prior to and during 7 months after transplantation. The mutant (sick) mice that received hUCB cells showed increased enzyme activity levels after transplantation. A decrease in stereotypical disease-related activity and an improvement in cognitive function were noted in the mutant mice, mostly in females.

Studies to determine distribution and types (a stem cell may mature into one of various types) of the hUCB cells transplanted into the *Naglu* mice have begun. Preliminary results show hUCB cells migrated to many structures of the brain, differentiated into neural and neuronal cell types. Our initial studies for evaluating neuron condition in the brain and glycosaminoglycans (such as heparan sulfate) in the tissues (liver) have been performed. We have identified improved neuronal architecture and reduced glycosaminoglycans in the liver of *Naglu* mutant mice, 7 mo. after hUCB cell administration.

Our results demonstrate that hUCB cells administered into brains of 1 mo. old *Naglu* mice have potential for delivery of the deficient enzyme. The increased enzyme activity, behavioral improvement, survival and neural differentiation of hUCB cells after long-term (7 mo.) transplantation, normal appearance of neuron architecture in the brain, and reduced glycosaminoglycans in the liver of *Naglu* mutant mice indicate the benefits of hUCB cells. However, behavioral differences noted between male and female mice require additional investigations. Additionally, frequent measures of enzyme activity might be helpful in determining hUCB benefits. Moreover, the administration of hUCB cells into the blood circuitry of mutant mice may be more beneficial and lead to the development of a new strategy for enzyme replacement for Sanfilippo.

Institute of Molecular Medicine and Genetics, Medical College of Georgia May, 2003

During the past year, we attempted to address some issues related to the success of an eventual stem cell transplantation-based therapy for the treatment of Sanfilippo. The first issue arose from recent literature that suggests that stem cell transplantation may work better in

the face of traumatic brain injury than in non-injured brains. We attempted to determine whether the pathology associated with Sanfilippo disease might analogously improve the chances for transplantation success in mice whose brains have fully developed. Interestingly, there appears to be something peculiar about the *traumatic* brain injury, as opposed to the chronic brain insults associated with Sanfilippo disease, which improves the chances for transplantation success. We are in the process of finding out the peculiarity of the traumatic brain in order to improve the chance for successfully transplanting cells in the brain of animal models of Sanfilippo disease.

We next focused our attention toward improving the chances of transplantation success by using a particular category of stem cell, the embryonic stem cell, for transplantation. We have been studying mouse embryonic stem cells for the past few years, trying to optimize the conditions under which they are compelled to differentiate, in order to improve the chances of transplantation success, while trying to minimize the odds of adverse effects. We have transplanted embryonic stem cells that had been induced to differentiate into neurons, into normal mouse brains, and our initial results look very promising. We saw evidence of the donor cells, and we saw no overt problems associated with these transplants in these mice. At this time, we are continuing to characterize the transplant, and have been constantly improving the conditions we use to differentiate these cells to see whether this will improve the chances for success. We have also shown that we can genetically modify these embryonic stem cells, a step that may become necessary to eventually sufficiently treat the disease. Altogether, these studies have provided a strong foundation for our development of a stem-cell transplantation therapy approach for the treatment of Sanfilippo disease. We intend to continue this research, while expanding our research into the use of human embryonic stem cells, in anticipation of eventual human therapy for this disease. We have already received human embryonic stem cells that have been approved by NIH for use in transplantation therapy. The next few years will prove to be crucial in our experimental work, which is progressing well and should yield interesting results.

UCLA
May, 2003

Using a mouse model of the Sanfilippo syndrome type B (MPS III B) that we developed four years ago, we have been trying to understand why the brain deteriorates in this disease and what can be done to treat it. Although there is no question that lack of alpha-N-acetylglucosaminidase activity is the primary cause of the Sanfilippo syndrome type B, there are many abnormalities that are secondary but nevertheless important contributors to the brain disease. One of these is the activation of brain cells known as "microglia," which are related to the immune system. The microglia show telltale signs of inflammation, such as expressing certain specific genes and proteins, long before there are any observed behavioral changes or clinical problems in the mouse. We believe that the activated microglia produce substances that are toxic to the neurons (nerve cells) and thereby exacerbate the disease process. If this hypothesis is correct, it is possible that certain anti-inflammatory drugs could alleviate some problems of the disease. This work, which The Children's Medical Research Foundation helped support, was published in the Proceedings of the National Academy of Sciences, issue of February 18, 2003.

However, really effective treatment would require replacing the missing enzyme. But therapeutic enzyme is excluded from the brain because of the blood-brain barrier (BBB). The BBB is nature's way to protect the brain from potentially harmful substances, but for the Sanfilippo syndrome, it presents the major obstacle to therapy. Our plans for the coming years are both to study and to outwit the BBB, in order to develop effective treatment of the Sanfilippo syndrome.

FUNDRAISING IDEAS

A Match For Kirby

Does your company have a matching gift program? It could double your support of the Foundation.

United Way Can Be For Kirby, Too

Does your company have United Way pledges at your workplace? Although we are not a United Way member, you can designate The Children's Medical Research Foundation as your recipient, and the funds will be forwarded to us through the United Way Campaign! Our United Way Chicago "Agency Number" is 3025558. For those of you out of state wishing to participate, please supply your local United Way agency with the Foundation name, address and our Federal ID #36-4033667.

Our thanks to the employees of Fidelity, SBC Ameritech, Wellpoint Health Networks, Inc. and David Mendenhall of San Diego, CA.

Give Kirby Security

Tired of taxes? The Foundation now has a brokerage account available that allows you to donate appreciated securities. Why pay tax on the gains when you can realize a charitable deduction of the full market value of your stocks…and it's for Kirby, too! Contact Brad or Sue Wilson at (708) 784-0631 to learn more.

Celebrate, And Make It For Kirby

Is there a special birthday coming up for a family member or friend? Are you looking for an alternative to the typical "over the hill" gift? Be different. In lieu of gifts, donate to The Children's Medical Research Foundation. Kirby always loves a party!

A Gift Like No Other

This holiday season give clients a donation to The Children's Medical Research Foundation in their name. It's a gift that won't gather dust and goes far beyond any other.

Go Kasual For Kirby

Tired of wearing those heels, hose or ties five days a week? Why not suggest a **"Go Kasual for Kirby Day"** to your employer? It's a great way to give a "relaxing feel" to a workday and raise funds for the Foundation. Simply send a memo to co-workers explaining the day and set the "fee" to participate.

Still in school but want to help? How about a **"Hat Day"** done the same way! It's fun for the kids and a great way for them to participate in a good cause. No "fee," just leave an amount up to them.

SAVE THE DATE:

9th Annual Sweetheart Dinner Dance

Plans will soon be underway for the 9th Annual Sweetheart Dinner Dance to be held February 6, 2004, at The Drake Hotel in Chicago.

Reservations will be $200 per person and must be made in advance.

Please contact the Foundation at (708) 784-0631 for further details and to learn how you can help to make it a "sweetheart" of a night for Kirby and others like her.

The Children's Medical Research Foundation, Inc.®

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