

# MSUD NEWSLETTER

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*Editor's Note: Dr. Downes will be presenting his research at the MSUD Symposium in June.*

## Zebrafish: A New Animal Model for MSUD

Written by Michael Koons

Researchers Friedrich, Lambert, Masino and Downes recently published a description of their work with zebrafish in the scientific journal *Disease Models and Mechanisms*. The group identified mutants which have a defect in the Branched-Chain alpha Keto acid Dehydrogenase (BCKD) enzyme complex. The *dbt* gene is essential to make the BCKD enzyme complex. In humans, mutation of the *dbt* gene can cause MSUD, a disorder of branched-chain amino acid metabolism, that if untreated can result in abnormal amino acid levels, seizures, neurological damage, and death. The zebrafish with this mutation demonstrate abnormal movements, which is linked to defects in metabolism and central nervous system function. Since these zebrafish display similar behavioral and metabolic traits to MSUD affected individuals, this system can be used as a model to better understand MSUD and identify new therapeutic compounds.

Zebrafish are used in university and pharmaceutical laboratories around the world to better understand and develop therapeutics

*(Zebrafish cont. on page 2)*

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**16th BIENNIAL  
MSUD SYMPOSIUM  
June 28 - 30, 2012**

I can't believe that almost two years have passed and it is time for another MSUD Symposium! I am especially excited about this conference, because there is enough interest in MSUD research to designate it the main focus of the symposium. Speakers already confirmed to discuss research medical and dietary issues, and liver transplantation are listed inside this issue.

Looking forward to seeing you all there!  
Sandy Bulcher

Check the MSUD website [www.msud-support.org](http://www.msud-support.org) frequently for informational updates.

See pages 4 & 5 of this newsletter



(Zebrafish cont. from page 1)

for many different human diseases. In this study led by the Downes laboratory, which was supported by grants from the National Institute of Neurological Disease and Stroke, a specific zebrafish mutant was examined that displayed abnormal movement and inability to swim caused by abnormal nervous system function. The research team determined that this zebrafish mutant contains a mutation in the dbt gene, which is essential to produce the BCKD complex. The abnormal movement performed by these zebrafish is thought to be similar to the seizures MSUD-affected individuals demonstrate during periods of severe metabolic distress.

These zebrafish mutants display abnormal amino acid levels, similar to untreated MSUD patients, and they were also shown to contain reduced levels of the neurotransmitter glutamate. Glutamate is known to be important for nervous system function in many different species, including humans, and abnormal glutamate levels have been found in other animal models of MSUD. Abnormal glutamate levels may be a key factor triggering the seizures caused by untreated MSUD.

In a December 2011 interview, Dr. Downes discussed some of his laboratory's plans to use zebrafish to better understand and develop therapeutics for MSUD. The small size, rapid growth, robust behavior, and ability to use sophisticated genetics make zebrafish an attractive candidate as an animal model. During the discussion, Dr. Downes outlined a few of the research questions he and his colleagues plan to address over the next several months:

#### **Can MSUD zebrafish be treated by restoring normal gene function?**

MSUD in humans can be treated by transplanting livers that have normal gene function. A similar approach can be performed in zebrafish by restoring normal dbt gene function in liver to assess whether this results in normal metabolism, nervous system function, and behavior. The next step would be to restore gene function in different tissues to assess whether other organs can also compensate for mutation of dbt, which could point the way towards new strategies to treat MSUD.

#### **Can MSUD zebrafish be treated using known pharmacological compounds?**

Small molecular compounds, such as phenyl butyrate or norleucine, are therapeutic compounds currently being studied for their potential to treat MSUD. These and other compounds can be applied to MSUD zebrafish to examine effects upon movement and metabolism. Since zebrafish are small, plentiful, and drugs can be easily applied, the next step would be to systematically test hundreds of additional compounds to identify new MSUD therapeutics.

#### **This animal model only represents a specific form of MSUD. Can this animal model be used to study other forms of MSUD?**

Other forms of MSUD occur from separate mutations within other genes involved with producing additional parts of the BCKD complex. This would be similar to number of different parts needed to produce a working, complex automobile, with all the parts needing to be at least somewhat functional to allow for driving. Damages to different parts of the vehicle still produce a broken-down car, but in different variations. The genes required to produce other portions of the zebrafish BCKD complex can be targeted to rapidly model other forms of MSUD (for example targeting mutations to other portions of the BCKD complex, including the E1<sub>α</sub>, E1<sub>β</sub>, or E3 subunits). ■

For more information, please see:

<http://dmm.biologists.org/content/early/2011/11/01/dmm.008383>

<http://www.bio.umass.edu/biology/downes/>

<http://www.fishforscience.com/model-organisms/why-zebrafish>

Or contact: Gerald B. Downes, Ph.D.

Assistant Professor, Biology Department  
University of Massachusetts- Amherst  
427 Morrill Building 2 (611 North Pleasant Street)  
Amherst, Massachusetts 01003, U.S.A.  
[gbdowes@bio.umass.edu](mailto:gbdowes@bio.umass.edu)



Another successful basketball season for captain Elan Geffen (transplanted Jan 06) and coaches Adrienne & Irv. Xtreme Team wins the Silver Medal and new women's team, Shining Stars, come in 4th place at the Florida State Special Olympics Competition in Cocoa Beach, FL.



## Research Update: Brain Chemistry, Chronic Symptoms in MSUD, and Liver Transplantation

by Emilie Muelly, PhD

Penn State Hershey Medical Center

A research study at the Hershey Medical Center, done in collaboration with doctors at the Clinic for Special Children, is yielding new information about the underlying mechanisms of MSUD. Our study

focuses on the serious chronic problems these patients face, including impaired problem solving and verbal skills, inattention, depression, and anxiety, and their relationship to brain chemistry. There is a large degree of variability with regards to these chronic symptoms in MSUD patients; some may be symptom-free whereas others suffer from debilitating psychological problems throughout adolescent and adult life. Our results confirmed that the overall prevalence of mental health problems is increased in MSUD patients.

Using Magnetic Resonance Imaging (MRI) technology, we were able to quantify chemicals in different regions of the brain based on different electromagnetic properties of these chemicals. Overall, MSUD patients demonstrated lower levels of glutamate, an important neurotransmitter used in cell signaling, and N-acetylaspartate and creatine, two energy molecules within the brain. We found correlations between specific neurochemical patterns and mental health problems. This suggests that the altered neurochemistry resulting from elevated amino acid and ketoacid levels could account for chronic psychiatric symptoms. Such findings emphasize the importance of ongoing, life-long metabolic control.

We also looked at the effects of liver transplantation on measures taken in our study. The size of our study was limited (11 patients post-transplant), but transplanted patients showed no difference in brain neurochemistry or chronic symptoms compared to those still on diet therapy. This does not undermine the value of liver transplantation with regards to preventing life-threatening metabolic crises, but shows that serious mental health problems present before transplant do not necessarily resolve afterward. This suggests that the timing of transplant might be important with regard to preventing long-term mental health problems and it also indicates that these problems may be rooted in subtle abnormalities of brain development that are not easily reversed.

We hope to publish the results of this study soon. More details on our findings will be presented at the MSUD Symposium in Philadelphia in June. Finally, we thank the MSUD patients and families who participated in our study; this research leading to a better understanding of MSUD could not have taken place without you! The research continues; next, we will use the gathered data to look into structural and connective features of the brain as they relate to neurochemistry and neuropsychiatric symptoms. ■

**Have you or your child reached an important milestone? Graduation from grade school, high school or college? Confirmation or Bar/Bat Mitzvah? Marriage or children? Please let us know so we can announce it in our next newsletter!**

## Interpreting Health Information

Gone are the days when all health information is obtained from your trusted family physician. These days, health information is just a “Google” away. But how do we know if the information we read or hear about is accurate and if it applies to us? It’s not always easy, as on-line articles are often not peer-reviewed, a process which allows scientists with knowledge in a given area the opportunity to review a paper for accuracy before it is published. What’s more, many websites have commercial interests which are not always apparent.

The Genetic Alliance has developed a “Trust It or Trash It” tool to help us out. Before deciding that your source is reputable, ask the following questions:

•**Who said it?** – It’s important to consider whether the writer/speaker is qualified to speak on the subject, as well as who paid for the piece or research.

•**When did they say it?** – It’s also important to know when something was written or updated, especially in fields that change very quickly.

•**How did they know?** – Determine whether the information pertains to you, and if it seems reasonable based on what you already know. Make sure that any research referred to was actually done on people with MSUD.

# 16th BIENNIAL MSUD SYMPOSIUM

**Location:** Embassy Suites Philadelphia Airport (the hotel is located one mile from Philadelphia International Airport)  
9000 Bartram Ave, Philadelphia, PA 19153 / Phone 215-365-4500 / Fax 215-365-3195  
Website: [www.philadelphiaairport.embassysuites.com](http://www.philadelphiaairport.embassysuites.com)

**Cost:** We are pleased that once again the MSUD Family Support group is able to host the conference without cost to families, professionals, or exhibitors. Annual dues will be accepted.

**Registration:** While there is no cost to attend, it is important for us to have an accurate count of who is attending for planning purposes. Please fill out the registration form included in this mailing and return it by 5-27-2012 to: Sandy Bulcher- 9517 Big Bear Ave Powell, Ohio 43065. You can also go online to the MSUD website to register.

**Agenda:**

Thursday June 28th- 7 pm - 9 pm Registration/Reception (drinks and light snacks provided)

Friday June 29th- Buffet Breakfast 6 am - 8 am (for those staying at the Embassy Suites)

General Session 8 am - 4:30 pm Lunch Provided

Saturday June 30th- Buffet Breakfast 7 am - 9 am (for those staying at the Embassy Suites)

General Session 9 am - 4 pm Lunch Provided

**Speakers and topics confirmed as of January 10, 2012:**

**Mario Cabrera-Salazar** MD Genzyme Corporation, Framingham, MA - Gene Therapy

**Gerald Downes** PhD University of Massachusetts, Amherst, MA - MSUD in Zebrafish

**Ira Fox** MD Children's Hospital of Pittsburgh, Pittsburgh, PA- Hepatocyte Transplantation

**Dianne Frazier** RD, PhD University of North Carolina, Chapel Hill, NC-Evidence- Based Guidelines for Nutritional Management

**Susan Hutson** PhD Virginia Tech, Blacksburg, VA - MSUD Mouse Model

**Brendan Lee** MD, PhD Baylor College of Medicine, Houston, TX – Phenylbutyrate Study

**George Mazariegos** MD Children's Hospital of Pittsburgh, Pittsburgh, PA- Liver Transplantation

**Holmes Morton** MD Clinic for Special Children, Strasburg, PA - Medical Management

**Emilie Muelly** MD/PhD Program Penn State Hershey College of Medicine, Hershey, PA- Neurocognitive Effects of MSUD

**Kristen Vallieu** PhD University of Pittsburgh, Pittsburgh, PA - MSUD Mouse Model

**William Zinnanti** MD, PhD Stanford University Medical Center, Palo Alto, CA-Potential Use of Norleucine and Gabapentin in MSUD

**Hotel Rate and Accommodations:** The MSUD Family Support Group has reserved a block of rooms at a reduced rate of \$129 per night, which includes a buffet breakfast for all those staying in the room and nightly manager's reception (5:30 pm - 7:30 pm) with complimentary beverages and light snacks. The room rate is good for 3 days before and 3 days after the symposium. The Embassy Suites is an all-suite hotel. Each suite consists of two rooms and can sleep up to six people. The bedroom has two double beds or one king bed and the living room has a pull-out sofa. In addition, each room has a refrigerator, microwave, coffeemaker, and high speed Internet. The hotel also boasts a heated indoor pool, whirlpool, fitness center, onsite restaurant, free parking and 24 hour complimentary airport shuttle. Several wheel chair accessible rooms have been reserved and are available upon request.

<http://embassysuites.hilton.com/en/es/groups/personalized/P/PHLAPES-MSU-20120625/index.jhtml?> Everyone (except speakers) is responsible for making their own reservation. Hotel check- in is 3 pm and check- out is 12 noon.

**Meals:** Complimentary drinks and snacks will be provided for all attendees on Thursday evening 6/28. Breakfast is included in the cost of the room rate for all those staying at the Embassy Suites on Friday 6/29 and Saturday 6/30. Those not staying at the Embassy Suites will need to provide their own breakfast on those mornings. Lunch on Friday 6/29 and Saturday 6/30 will be provided free of charge to all attendees. Dinner is on your own on 6/28 through 6/30. Low protein food options will be available Thursday evening 6/28 during the reception and for breakfast and lunch on Friday 6/29 and Saturday 6/30.

# June 28 - 30, 2012 • Philadelphia, PA

**Attire:** Comfortable, casual attire is appropriate for the entire symposium

**Child Care Activity Room:** There will be a room available with activities/entertainment for children and, we hope to have several volunteers to assist the children. There will be no babysitting services, however. Please keep this in mind as you plan your trip. Consider bringing a grandparent, teenager, or sibling to babysit your younger children. Older children, teens, and young adults are encouraged to attend the general sessions.

**Directions to the hotel:**

*Traveling from the North,* follow I-95 South towards the Philadelphia International Airport and use exit #12B, Cargo City. At the stop light, turn right. The hotel will be on your right hand side.

*Traveling from the South,* follow I-95 North towards the Philadelphia International Airport and use exit #10, Cargo City. Proceed forward and at the first light, turn left onto Bartram Avenue. Travel one mile and the hotel will be on your right hand side.

**Shuttle Service:** If you would like to use the hotel's complimentary shuttle service from Philadelphia International Airport, please call the Embassy Suites front desk at 215-365-4500 upon your arrival at the airport and request the shuttle. Outside of Baggage Claim, meet the shuttle at the blue signs marked, "Hotel Courtesy Shuttle Pick Up Zone 4"

**Plan a family vacation:** The Eastwick train station is within walking distance of the hotel and provides access to downtown Philly and all of its wonderful sights. Or in conjunction with the symposium, plan a family vacation to other Eastern US cities.



***See you in Philly!***

Sandy Bulcher, Director of MSUD Family Support Group and Symposium Coordinator

**Don't forget to complete and send back your registration form and make your hotel reservation. If you have any questions, feel free to call me at 614-389-2739 or email at [dbulcher@aol.com](mailto:dbulcher@aol.com)**

*Special Thanks to the **United Service Foundation** for their generous donation which supports travel expenses for a limited number of MSUD families who would otherwise be unable to attend.*

## **FINANCIAL AID TO ATTEND MSUD SYMPOSIUM**

Our organization has been again blessed by a donation from the United Service Foundation. This money is given to provide funding for families who need financial aid in order to attend the MSUD Symposium this year. Please let us know as soon as possible if you are interested. First time attendees have priority and funds are limited. It is important that you only apply if the funding is needed to make it possible to attend. Our goal is to see that all interested persons have the opportunity to attend.

We are sorry but children with MSUD under 10 years of age or those older in poor health cannot be included in this assistance program when traveling from a distance. Long traveling time increases stress and may cause children with MSUD to become ill even to the point of needing medical treatment.

For those in countries outside the USA, it is important to begin the process of obtaining passports and visas promptly.

All interested persons please contact us at: [wjbrubacher@afo.net](mailto:wjbrubacher@afo.net) or call 574-862-2992.

Wayne and Joyce Brubacher



## Growing Up With MSUD

By Lindsey Nicole Miller

Growing up with MSUD wasn't easy, but I wasn't alone. My name is Lindsey Nicole Miller, born in 1986 at Lewistown Hospital in Pennsylvania. I'm the second child of three in my family, and the second child to have MSUD. I was diagnosed with MSUD on the second day after my birth. Since my brother Sean was already diagnosed with MSUD, I was on an immediate transfer to Children's Hospital of Philadelphia (CHOP) to be tested to see if I had this disease.

Having this medical condition, you realize how different and difficult your life is. I had it better because my parents already had practice and knew what precautions and restrictions were needed in order to raise a child with MSUD. For starters, I had Classic MSUD. Mom tells me that it is one of the worst of the three types of this kind, and that I need to monitor my diet daily, which is important. I am a picky eater, and have to drink formula every day. I am restricted to eating low protein foods and have to watch how much I eat. Although I didn't want to listen, Mom made sure that food was prepared and ready for anyone who baby sat my brother and me. It was a struggle for me. Eventually my sister was born in 1990 and by this time Pennsylvania was screening newborns for MSUD. I consider her lucky because she didn't have MSUD, but she has been a very supportive sister.

When I was 12, Mom heard of "Make- A- Wish Foundation". She contacted them, and they came to our house and granted my wish to go to Walt Disney World in Florida. I was so happy because I got to go visit another state and "Make- A- Wish" took care of all of our vacation needs. I loved staying at "Give Kids the World" Resort.

The same year, I was also diagnosed with a seizure disorder. My body was going through changes and that made my levels extremely high. At that time, I didn't understand what was causing this problem, but I was admitted to the Philadelphia Hospital. It's been years now since I have been hospitalized for seizures, and all I have to do is take medication.

My limitation did not stop my family from making my life a memorable one. We took trips to go camping, and I got to see the beach and the ocean. All we had to do was prepare for the overnight and the wake up. I always had to take my formula and the ingredients to make the formula. At restaurants, if we went out everyone knew what I was going to order. Even if I tried to change, I didn't have much of a variety to choose from. If you were to talk to my friends from high school, they would have said I appeared normal and they couldn't tell I had a medical condition. Hearing that made me feel good.

Growing up and graduating from high school was one accomplishment, but I knew I wanted to go to college. In 2006, I started at South Hills School of Business and Technology. I have my Associates degree in Office Technology Professional. I also worked at an internship at Mifflin County Courthouse which opened the door to work at Highmark Inc. I have been working there for the last three years. I also work at the Port Royal Speedway. All my co-workers are very supportive of my medical condition and help with my care.

For a long time, the only person I knew who had MSUD was my brother. Then in 2008, I went to my first symposium and to my surprise I met new friends that had my same medical condition. I now keep in touch with them through the internet. We talk and share views about our illness.

*(Lindsey cont. on page 7)*

(Lindsey cont. from page 6)

Having MSUD doesn't stop me from expressing my feelings. I write poems, and I have done this since the year 2000. It's a good stress reliever to express how I feel through my writing. I get to show my family and friends my talent. Every so often, I will spend five minutes to an hour writing how I feel. I enter contests and had two poems published in two different books. Even though in high school participating in sports wasn't easy, I excelled at writing poetry. I entered a recent contest, and this is the poem I entered:

### Hiding It Well"

I can hide it just as well  
Oh, can you not tell  
I'm juggling between  
I love you and not  
Don't you see I'm good at it  
Oh, I can hide it just as well  
I know what to tell you  
Just so you don't see how I feel inside  
How I feel inside is so much more  
But I can hide it all from you I'm sure  
But until you show me you won't see me  
Oh, you will not ever see me at all.

(April 18, 2010)

In winter 2007, I had to be hospitalized for having the flu which made my levels high. I was admitted to CHOP in Philadelphia. I was in the hospital until my level went down. On the way home from the hospital, mom asked me "It's not going to get better, is it?"

I told her "No, it's never going to be right with the hospital, either my levels are too high or too low." She proceeded to ask me if I wanted a transplant. My response right away was yes!!!! Mom told me as long as I set everything up to get on the transplant list and plan the visits, then she will support me no matter what.

In 2008, I went for a week to Pittsburgh for a consultation visit. They explained everything in detail with a lot of information and pictures. I met a lot of doctors who explained the good and the bad points of a transplant. Then they took twenty-one tubes of blood after the visit. After visiting Pittsburgh for a week, I was eventually placed on the list and now I'm waiting for the call.

If I have ever had any memorable moments in Philadelphia, it would have been over a July 4th weekend one year. My brother and I both had high levels, so Philadelphia Hospital wanted us admitted. While I was hospitalized, I went and wondered the halls. I wound up meeting a friend there named Kristy. In the hospital, there was a computer room where we could go to get on the computer. We were a foot away having a chat conversation on the computer. On July 2nd, we all came to my room to see fireworks out my hospital room window. It was my brother, me, Kristy, our monitors, and our nurses. It was great because the next day I was on my way home from the hospital.

Although I continue to wait for a transplant while living with MSUD, things are going really well with my life. My family, friends and co-workers give me all the love and support I could ask for. Next spring, I plan to get a place of my own which I am really excited about. I am planning to travel to various states next summer. And I'm really looking forward to meeting up with many of my friends at the next MSUD Symposium in my own state of Pennsylvania late June 2012. I couldn't be happier! ■

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## Make-A-Wish Foundation

I'm Lindsey Nicole Miller, and I wrote the article, "Growing Up With MSUD." Well I also want to go into detail about how thankful I was and will always be, to get my wish to go to Walt Disney World in Florida. Around 1997 when I was eleven years old, my mother heard about the Make-A-Wish Foundation from Children's Hospital of Philadelphia. My mother talked it over with my father and then gave them a call. Two ladies from the foundation came to our house and explained the program to mom and dad. They asked us questions about ourselves and where I wanted to go. At the time, I didn't know what I wanted or what trip would be the most memorable. The ladies told us what some other people chose for their wishes. I finally chose to go to Walt Disney World in Florida.

In October, our family was off to Florida. When we arrived, we got our luggage and rental car and drove to Kissimmee to "Give Kids the World" where we stayed. It was like a village. We had our own cottage place to come back to after we went to the parks. We got to go all expense paid to Disney World, MGM, Sea World and Animal Kingdom parks. Every morning, we had a place to go eat as much as we wanted which was fun. The best part was at night... we swam in the heated pool. We also went on rides at the park without standing in any lines and got autographs from Mickey Mouse, Minnie Mouse and a lot more Disney friends.

The trip went too fast but we took a lot of pictures. We have a lot of good memories from our time at Walt Disney World, and it would be great to go back.

# Britney Marie Page - 9/6/1992 - 1/20/2011

By Laurie Page, Mom



**Britney** spent the first nine years of her life in and out of the hospital. She had been relatively healthy for the last nine years. Until Christmas Eve 2010. Our traditional celebration started out normal, skating on the lake in the early afternoon, opening presents in late afternoon and a festive dinner to end the day. Britney loved to cook especially during the holiday season. She insisted that the table be set with crystal, china, etc as lavishly as she could make it.

That evening Britney began vomiting and life as we knew it ended forever. She spent the last few weeks of her life in the PICU at the University of Michigan Mott's Children Hospital. She fought valiantly. During the first few days she sang the Michigan victors song with the U of M team athletes that came to visit her; joked with the doctors and nurses, chatted with her boyfriend and was our usual happy Britney. Coincidentally, her boyfriend was on the same floor recovering from surgery and at one point was even a few beds away in the PICU. Her condition was deteriorating and she suffered numerous respiratory arrests. She was put into an induced coma to give her brain a chance to recover but that was not to be. She succumbed to the effects of MSUD and on January 20, 2011 surrounded by her family and friends we lost our wonderful, darling Britney.

Britney's nickname was sunshine, a name her mother gave her as a baby because she always radiated this happy little glow. She grew up to be a beautiful, loving young lady. She loved unconditionally and only saw the good in people. She never let MSUD get her down even though she suffered from almost every ill effect of the disease. Britney loved swimming, tubing, knee boarding, fishing, hunting and watching her favorite show NCIS. She even bagged an 8 point buck on her first day of hunting with her dad.

When she was 10, Britney was featured in the Meade-Johnson calendar. Ironically she was pictured in the month of January. We tried very hard to make sure that she was able to see and do as much as possible. She vacationed in Paradise Island, Hawaii, Disneyworld, Gatlenberg, and several smaller excursions around Michigan including Mackinac Island. Our last vacation was to Williamsburg and the surrounding areas where we were all treated to VIP passes to Busch Gardens and Water Country, USA.

Brit was really looking forward to Prom and graduation. In fact, she had been planning both for almost a year. She had accumulated enough credits to graduate and her sister, Amanda, accepted her diploma during the graduation ceremony. Her classmates carried flowers and gave her a moving tribute that brought tears to the entire auditorium.

It has been amazing to listen to the large numbers of people who have said that Britney made a profound difference in their lives and how she showed them what was and was not important. She made such an impact on the hospital personnel that several of her doctors attended her memorial service along with more than 100 friends and family.

We added some new traditions to our Christmas celebration this year. Before dinner, we lit candles, one for each letter of her name, and recited this poem...

Britney was our sunshine, the light of our lives. We painfully miss her laughter and zest for life. There will forever be a void in the lives of all who knew and loved her. She will forever be in our hearts.

*Britney's obituary and guest book may be seen by going to Google and typing 'Britney Marie Page'.*

Let this be a loving reminder  
That someone is missing today,  
Someone our hearts still hold on to,  
As we travel along life's way.  
Someone who made life so special,  
Someone who gather here,  
for all those who won't be forgotten,  
But cherished from year to year.  
And now as we pause to remember,  
Let us all fondly recall,  
How dearly each of us loved her,  
And oh....how she loved us all.





# The Koons Family Story

By Jamie Koons, wife of Mike Koons

Bonnie and Dave Koons have learned a lot about MSUD over the years, since their two sons both have mild variant forms of the disease. The Koons children were diagnosed in the early 1980's. Matt (31) and Mike (30) are now grown and healthy, and their family credits the doctors at Children's Hospital of Philadelphia (CHOP) and the support they received from other MSUD families. Bonnie and Dave's first son, Matt, was diagnosed at 13 months old, when Bonnie was 7 months pregnant with Mike. Up until the diagnosis, his condition was a puzzle to his family and his local doctors.

"My greatest fear was not that he was physically sick – it was that he was developmentally delayed and no one knew why," Bonnie said. "For the first six months, we were told to just watch and see. When he was a year old, we were getting ready to line up a series of tests, but then he had a seizure."

The seizure landed Matt in Polyclinic Hospital in Harrisburg. They ran many tests, including a screen for MSUD, but the result was a false negative. Bonnie and Dave learned the issue was probably metabolic, and a visit to CHOP was recommended. Bonnie distinctly remembers what happened at the first CHOP appointment. Dr. Marc Yudkoff took Matt's diaper off and sniffed it. He then started shredding the insides of the diaper and stuffed bits of it into a syringe. He knew what was wrong immediately. Blood tests were done and the doctor put him on MSUD formula right away. "It was a huge relief at first to know what was wrong, but that feeling quickly turned to fear," said Bonnie. "It was a disease that no one had ever heard of, and I had no idea how to take care of him."

A couple months later, Mike was born at University of Pennsylvania and quickly transferred to CHOP. Mike was officially diagnosed within the first week of life, and stayed at CHOP for two weeks. He did well and the family went home to Harrisburg. Soon after Mike's birth, Matt became very sick with a virus. Bonnie quickly learned that children with MSUD have severe reactions to viruses or even bad colds. Their metabolic levels would rise to the point of being toxic and life threatening.

When the boys were young, the family made the 2.5 hour drive to CHOP about every two weeks and then, gradually, once a month. It was several years until the boys graduated to annual visits.

The boys simply didn't care about eating, which was one of the biggest challenges for Bonnie, who was of course concerned about their nutrition. What bothered the boys the most were the constant hospital visits, which were often exhausting experiences for the whole family. Since the boys were not at an age where they could communicate exactly what hurt, the family watched their every move. Bonnie remembers Dr. Yudkoff telling her, "You will be their doctor at home."

She had looked up MSUD in the dictionary, and all it said was "usually fatal." After that terrifying discovery, there



Dave & Bonnie Koons with grandson Simon Carl

was nothing left to do but more research. All the information was mostly in medical terminology, and there was no Internet at that time with its various, more readable sources. "I didn't think I could do it," said Bonnie. "Everyone in our families was very supportive, but no one knew anything about MSUD. That was the reason I got so involved with the support group."

## FAMILY SUPPORT GROUP

At CHOP, the doctors gave Bonnie the name of Mary Katherine Martin. She lived in New Holland, Lancaster County, and her two children had classic MSUD, and were very close in age to Bonnie's boys. Bonnie called her and talked with her for a very long time. The Martin family came to visit Bonnie and the boys in Harrisburg within a few days. The two women were able to commiserate over their shared experiences.

The Koons' met many Mennonite families with MSUD, and started a local support group so everyone from different cultures could come together for the common good. Bonnie organized the first picnic in Linglestown, PA for the family support group. It was a success, and many families from all across PA were able to attend.

Bonnie met Joyce Brubacher, head of the national support group, at another family's home, and corresponded with her in order to help with the national newsletter and support group. Bonnie accepted the position of Family Contact through Joyce. Families with newly diagnosed children would be given the family support group contact

(Koons cont. on page 10)

(Koons cont. from page 9)

information by the hospital. Bonnie sent out the information packet the support group had developed and at times called the family to talk and answer any questions they had. The information packets put medical information about MSUD in laymen's terms. Medical terms were explained in a glossary so that the families could understand what they were dealing with. The group had the help of Alice Mazur (RN, PNP), the Koons family's nurse specialist, in this important project.

Bonnie made another important contribution by spearheading a cookbook fundraiser. She gathered recipes from MSUD families and friends. The cookbook had a section with low protein recipes in it, and was first printed in March of 1988.

Alice Mazur remained an important figure in the Koons' lives. In addition to providing the family with information, Mazur gave them the support they needed. "I knew that when I got her on the phone, everything would be okay," said Bonnie.

When Mike was a junior in high school, he developed severe gastroenteritis, and became dehydrated to the point of instability. He ended up hospitalized at CHOP for a week and a half. Bonnie and Dave thought they may lose him, but he slowly regained his health.

"It doesn't take a lot for an illness to snowball," said Bonnie. "That's why the boys have to be vigilant about what they eat, so they can stay as healthy as they can to stave off anything opportunistic."

## BIRTH SCREENINGS

Pennsylvania had more incidences of MSUD than anywhere else in the world, but in the 1980's the state didn't screen for the disease at birth. Individuals from the support group began writing in February of 1987 to their state representatives to push for legislation mandating MSUD screenings at birth. Bonnie gathered statistics on the significant cost of care of a child with undiagnosed MSUD, compared to the cost of a \$10 screening.

They met with challenges, and the wheels were grinding slow. The group was told by many people that their push for the screenings wouldn't work.

At the time, Bonnie was having a lot of emotional issues due to the stress of having two children with MSUD. She started seeing a counselor, whose husband was investigative reporter Sandy Starobin. Sandy worked for the radio station KYW News in Philadelphia. He broke huge investigative stories, and he was very interested in starting a campaign to inform the public about the plight of MSUD families and to push for newborn screenings in PA. Bonnie's therapist asked her if she'd be willing to share her story with him, and Bonnie agreed. She served as a liaison between Starobin, the hospital, and the MSUD families. The campaign radio segments ran on both KYW News in Philadelphia and KDKA Pittsburgh.

At first, the campaign didn't work, so Starobin doubled his efforts and made an even stronger case, stressing that babies were dying unnecessarily in PA. It took years to pass, but the day finally came in July of 1990 when newborn screenings for MSUD were mandated in Pennsylvania. The Supplemental Newborn screening covered the following diseases: PKU, congenital hypothyroidism, cystic fibrosis, muscular dystrophy, galactosemia, congenital adrenal hyperplasia, biotinidase deficiency, hemoglobinopathies (includes sickle cell anemia), MSUD,



homocystinuria, glucose-thick-phosphate dehydrogenase deficiency, gamma glutamyl cycle disorders.

"Finally – some infants will be saved," said Bonnie. "I always told Sandy that if one baby was saved, all of this was worth it. It was a wonderful feeling to know that these little ones could grow up healthy."

Of all of his stories, Starobin told friends and colleagues that he was most proud of his work to initiate newborn screenings for MSUD.

## PRESENT DAY

Bonnie feels very lucky that both of her boys accepted their disease and continue to take care of themselves to this day.

"I'm so proud of them," she said. "It was so rough on them – it wasn't easy on any of us."

Mike grew up smaller than most kids, and started Taekwondo at a young age. Practicing martial arts made him stronger, physically and emotionally. He still practices Taekwondo and now owns a school, where he teaches at night in York, PA. He has a full-time job as a chemist, and recently earned his Master's degree in Chemistry.

When Matt was diagnosed, the doctor said he'd probably be able to walk and talk, but he probably wouldn't be able to ride a bike or do other typical things that children do.

"Look at the man he's become," said Bonnie. "Matt became a very compassionate individual. He sees others' pain and is empathetic to it."

Matt has training in Computer Science and currently works for the Patriot-News in Mechanicsburg, PA as a Reader Services Representative.

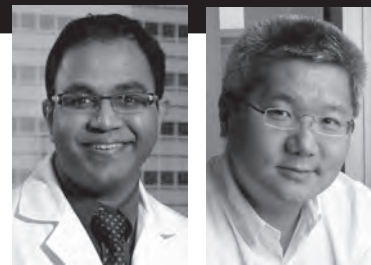
"No matter how bleak of a story these kids can have, you never know what can transpire," said Dave. "Bonnie didn't think she'd ever have grandchildren." Mike and his wife now have a healthy, active son

(Koons cont. on page 11)

## Phenylbutyrate Therapy to Decrease Branched Chain Amino Acids and Branched Chain Keto-Acids in Subjects With Maple Syrup Urine Disease

Sandesh C.Sreenath Nagamani, M.D. and Brendan Lee, M.D., Ph.D.

The metabolic management of patients with maple syrup urine disease (MSUD) presently consists of dietary management that provides sufficient protein, amino acids, and other nutrients required for normal growth while preventing increases in the plasma levels of the branched chain amino acids (BCAA) leucine, isoleucine and valine and their respective branched chain keto-acids (BCKA). Currently, there is no medication that can decrease the levels of these branched chain amino acids in patients with MSUD.



We have extensive experience in the research and management of a group of metabolic disorders called urea cycle disorders (UCD). The urea cycle is a pathway in which the nitrogen present in proteins and amino acids is converted to a product called urea which is then excreted in the urine. Patients with UCD are unable to make this conversion. The result is an elevation of the toxic nitrogen containing compound ammonia. To decrease the load of nitrogen on the defective urea cycle and to scavenge the amino acid nitrogen by alternative routes, many UCD patients are treated with a medication called sodium phenylbutyrate. We noted that this medication in addition to preventing elevations of ammonia in UCD patients also led to a decrease in their plasma BCAA. Our finding was independently confirmed by a large cross sectional study involving patients from all over the United States. These observations have lead us to ask two important questions 1) Could therapy with sodium phenylbutyrate lead to a decrease in BCAA in patients with MSUD? 2) What are the mechanisms by which this medication leads to a decrease in BCAA?

To answer these questions, we conducted a pilot study with three healthy subjects and five subjects with MSUD. Treatment with sodium phenylbutyrate resulted in a decrease in BCAA and BCKA in both the control and MSUD subjects. By detailed studies involving humans and mice, we showed that the medication modulates the activity of an enzyme (BCKDC kinase) that regulates the activity of the enzyme that is deficient in MSUD (BCKDC). Treatment with sodium phenylbutyrate increased the residual enzyme activity thus leading to a decrease in BCAA and BCKD in MSUD.

In order to validate these findings in a larger cohort of patients and to evaluate whether sodium phenylbutyrate could be a treatment option in patients with MSUD, we are conducting a clinical trial at Texas Children's Hospital and Baylor College of Medicine, Houston TX. In this trial, subjects

with MSUD will be enrolled and started on treatment with either sodium phenylbutyrate or placebo for two weeks. They will be then switched to the other arm of the study for another two weeks. As an example, if a subject receives placebo during the first two weeks (days 1 to 14) of the study, they will be switched over to receive the drug for the next two weeks (days 15-28) or vice versa. The levels of BCAA and BCKA will be measured at the end of each arm of the study to evaluate whether treatment with the drug leads to a decrease in BCAA and BCKA as compared to the placebo in these subjects. The medication is likely to increase the residual enzyme activity by modulating the E1 alpha component of BCKDC. Hence, we expect that patients with mutations in the E2 component and intact E1 alpha subcomponent would respond in a more favorable fashion. However, it is possible that even patients with mutations in E1 alpha subcomponent may respond. We will hence enroll patients with the classic, intermediate, intermittent forms of MSUD with mutations in either E1 alpha or E2 subunits. We will also test whether we can develop approaches to predict patients who may respond to such a therapy if successful.

This is the first trial exploring a medication for patients with MSUD and may lead to a novel therapeutic option in the management of these patients. This clinical trial and research project is supported by the National Institute of Diabetes and Digestive and Kidney Diseases. The work is taking place at Baylor College of Medicine (Drs. Brendan Lee and Sandesh Sreenath-Nagamani), University of Texas Southwestern Medical Center (Drs. David Chuang and Richard Wynn), and Virginia Tech (Dr. Susan Hutson). We will be enrolling patients by the end of the year 2012. Those interested in participating may contact Ms. Mary Mullins, research nurse coordinator for the study at 832-822-4263. ■

(Koons cont. from page 10)

Simon Carl Koons, who is almost three years old. He does not have MSUD.

Reflecting back, Bonnie has a message for new parents of children with MSUD. "It's important not to dwell in the past. Try not to worry about the future – although I know that's easier said than done. Just live in the day, do the best you can, and love your child. Reach out to others who understand what you're going through. Don't alienate yourself. Become involved with another family or support group with others facing the same challenges."

Dave said that Bonnie is "much stronger than she ever thought she was. You can do more than you think you can do."

Bonnie and Dave are so pleased with how both of their boys turned out, and extremely grateful for their continued health. Bonnie said, "I think that every child is a gift from God." ■



## Fruit Dip

Good, easy recipe that the whole family can enjoy!

- 1 can (21 oz) apple pie filling
- 1/2 cup orange juice
- 1 cup Cool Whip Whipped Topping

Combine pie filling and orange juice in blender, blend until smooth. Fold in whipped topping. Serve with low protein baked goods or fruit.

Makes 24 servings  
Serving size is 2 tablespoons  
4mg leucine per serving

Please send recipes to  
Food News Editor

Glenda Groff  
515 W. Church Road, Ephrata, PA 17522  
Ph: 717-738-4793 • ernieglenda@dejazzd.com

## Hamburger & Cheese Sticky Buns

- |                             |                                     |
|-----------------------------|-------------------------------------|
| 2 dinner rolls, low protein | Sauce                               |
| 2 mushroom burgers          | 2 tablespoons butter                |
| 2 slices low protein cheese | 1 tablespoon brown sugar            |
|                             | 1/2 tablespoon Worcestershire sauce |
|                             | 1/2 tablespoon mustard              |
|                             | 1 teaspoon poppy seeds              |

Preheat oven to 350 degrees. Split rolls and layer burger and cheese on bottom of roll. Place the top part of the bun on top of the cheese. Place in a baking pan. Bring sauce ingredients to a boil and spoon over the top of the rolls. Bake covered for 5 minutes and uncover and bake 5 more minutes. 2 servings

Per sandwich	Protein	Leucine	Calories	Phe
	1 gram	124 mg	370 cal	85 mg

## Stuffed Zucchini

- |                          |   |
|--------------------------|---|
| 1 zucchini 8 inches long | 1/4 cup chopped onion                   |
| Salt and pepper          | 1/4 cup tomato sauce                    |
| 1 tablespoon butter      | 1 cup cubed low protein bread           |
| 1/4 cup chopped celery   | 2 tablespoons low protein cheese shreds |
| 1/4 cup shredded carrots |   |

Cook zucchini in boiling salt water for 5 minute. Cut in half lengthwise. Scoop out and discard seed cavity. Melt butter in skillet and sauté celery, onions and carrots until tender. Add tomato sauce and bread cubes. Toss together. Spoon into zucchini and place into a baking dish. Sprinkle with cheese and bake uncovered at 375 degrees for 30 minutes.

2 servings				
Per serving	Protein	Leucine	Calories	
	1.8g	76 mg	215	



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(for children 1 year to 10 years of age)

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## Cambrooke Foods – Winter/Spring 2012

**Cambrooke Foods** has expanded their low protein breakfast product line to include bagels and bagel bars. Try the new **Cinnamon Raisin, Onion and Plain Bagels**. If you like more of the grab and go bar format, check out the new **Bagel Bars**, available in French Toast and Mixed Fruit flavors. The French Toast bars have cinnamon drops and maple flavor and the Mixed Fruit bars are studded with raisins, apples and cranberries.



Visit **Cambrooke Foods** Facebook site and a Twitter pages. These interactive pages will give you a chance to create and join conversations about what is relative to you, learn more about Cambrooke's products and connect with others for recipes and product usage tips. You will have the opportunity to converse with a registered dietitian and become educated on a variety of concepts related to maintaining a healthy diet and lifestyle.

Contact Cambrooke if you have not had the opportunity to try the **Camino pro<sup>®</sup>** formula line of ready-to-use drinks for MSUD. Available in Fruit Punch or Pina Colada flavors with 15 grams of protein per serving.



Request your free **Camino pro<sup>®</sup>** samples or place your order today. Call toll-free, (866) 4 LOW PRO / (866) 456-9776 or visit our website at **www.cambrookefoods.com**. If this is not convenient, you can mail (4 Copeland Drive, Ayer, MA 01432), e-mail (orders@cambrookefoods.com) or fax at (978) 443 -1318.



## Are Low Protein Foods Available in your Local Grocery Store?

Shannon Mallory RD, LD  
Metabolic Dietitian  
Division of Molecular & Human Genetics  
Nationwide Children's Hospital  
Columbus, Ohio

This is the million dollar question... literally, if you are purchasing or have purchased low protein products from an on-line distributor. Low protein foods are expensive on-line, and there is usually a minimum amount which must be purchased before foods are shipped. Low protein foods made specifically for the inborn error of metabolism population are typically not available in local or chain grocery stores. That isn't to say it isn't possible though... a few savvy families have made arrangements with local grocers to have low protein goods shipped to the grocery store they frequent.

With changing dietary needs and demands of the entire U.S. population, new foods are showing up on grocery shelves daily. Entire aisles of chain grocery stores are dedicated to organic, gluten free and specialty foods. There are now more cows' milk alternatives than can be counted on two hands. Are some of these foods compatible with low protein diets? Absolutely! The challenging part is figuring out which ones are compatible with a low protein diet and how to count them in.

Gluten free products are sometimes lower protein alternative to their wheat or white starch counterparts. Gluten free products are readily available in most local grocery

chains- including most grain products (cereals, waffles, breads, crackers, etc.) and gluten free flours are useful to bake with. Gluten free flours to look for include tapioca, arrowroot, rice and potato flours. Some gluten free flours are higher in protein due to their amaranth or quinoa content (grain like crops which are higher in protein naturally, specifically lysine). So both label and ingredient list reading remains very important when using gluten free starch products.

Looking at dairy alternatives, rice and coconut milk are usually lower in protein than cow's milk. Almond milk and soy based products are typically not an option, as the protein content is generally higher than that of cow's milk. Dairy products have further evolved; into yogurt, ice cream and cheese products. Again, when looking at alternative dairy products to use in a low protein diet, avoiding soy is usually the first step. A brand of products which is coconut based (So Delicious) produces a variety of frozen coconut based ice creams which are very low in protein. Low protein cheeses have also expanded into cheese which are rice based (Rice Vegan) or cheese alternatives made from arrowroot and tapioca starch (Daiya brand shredded cheese).

In conclusion, label reading is still important- especially since some of these foods have not yet made it to low protein food lists or on-line databases. New foods can be used and calculated into a diet (talk over what new foods are being used with your metabolic dietitian and come up with some protein conversions such as 1 gram of protein= ~70mg of leucine for starch based foods). And, as always please, please email or call your friendly metabolic clinic dietitian with questions about new foods, or assistance calculating and determining how new foods will fit into a diet. ■

## Challenging the Paradigms: Liver Transplantation for Metabolic Disease

*Join specialists from Children's Hospital of Pittsburgh of the University of Pittsburgh Medical Center (UPMC) and distinguished faculty from around the world May 4-5, 2012, for a conference to explore the treatment of metabolic disease and the indications and outcomes of pediatric liver transplantation.*

**Friday, May 4,** is dedicated to scientific sessions. A panel of experts will discuss liver transplantation as an excellent approach to the treatment of certain types of metabolic disease, as the range of disorders suitable for this approach continues to evolve. The specific metabolic diseases to be addressed include maple syrup urine disease, urea cycle defects, propionic and methylmalonic acidemia, mitochondrial diseases, glycogen storage diseases and phenylketonuria.

**Thursday, May 5,** is Family Participation Day, which focuses on providing information for families whose children may have a metabolic disease, including a presentation of the risks of metabolic disease, quality of life concerns, and what families need to know when balancing the risks and benefits of liver transplantation for treatment.

For more information and to register, visit [www.chp.edu/metabolic2012](http://www.chp.edu/metabolic2012) <<http://www.chp.edu/metabolic2012>>  
**Sharon J. Mastro, Children's Hospital of Pittsburgh of UPMC / eMail: [Sharon.Mastro@chp.edu](mailto:Sharon.Mastro@chp.edu)**

# THE LIFE OF ZEKE ANTONY LEE HARRISON

## A PERSONAL STORY



1 year 3 months  
By Jazmin Harrison, Mom



My beautiful boy **Zeke** was born at Bendigo Base Hospital in Australia on December 7th, 2010 at 1:08pm after a difficult birth. When half his head was out the doctor saw that the umbilical cord was wrapped around his neck. He had to be pushed back in to unwrap the cord. Once my beautiful baby was born, I waited for the midwife to sweep him up and place him on my chest for our first cuddle, but he was taken away and put into an open humidicrib while a nurse told me not to panic. They called a code blue and about 15 doctors/nurses rushed in. As any mother would, I freaked out. I thought the worst - My baby was dead!! 8 terrifying and horrible minutes later I heard my baby cry!! It was the most invigorating feeling ever. Finally I had my first brief cuddle with Zeke who was a whopping 9 pound 10 ounces!!! He looked like a 4 month old. After about a minute the doctors whisked him away to the intensive care unit. I was told that Zeke was born dead, white as a ghost, which they say is the hardest case to revive. What a crazy start to such a precious life. After four days in intensive care we were finally allowed to go home, where my 3 year old son Jacob and husband Corey were anxiously waiting for us!!

The first night at home was tough. Zeke hardly slept. He would cry and cry and cry!! The next day he practically slept the entire day, waking up occasionally for a feed. My husband had a very busy work schedule so it was hard for him to help out, but when he was home he would take over so that I could have a bit of a sleep. On day 7 of life I was starting to get very worried! Zeke would hardly get 40cc's (about 1.5 ounces) of milk into him for the entire day, and had not pooped for 4 days. On December 14th, when Zeke was 8 days old, I had the phone call from Hell. The one that every Mother dreads!! A doctor from the Royal Children's Hospital rang me and said that there was something wrong with Zeke's heel prick test and that they had sent an ambulance to bring him to the local hospital. While we were on our way, Zeke stopped breathing off and on! We eventually arrived at the Emergency department where we were rushed into a cubicle and many doctors and nurses worked on him.

Finally I got some answers. A doctor told me that Zeke had a rare disease called Maple Syrup Urine Disease! I had never even heard of this disease and he also told me that no one there had ever heard of it before either. So here I was trusting my new baby's life in the hands of people who had never ever dealt with this disease before. Was very reassuring - NOT! After a few long hours of trying to get IV's into Zeke, the infant transport team arrived to transport us to the Royal Children's Hospital in Melbourne. When we arrived Zeke was rushed to the Neonatal Intensive care Unit. He was in a terrible state, and had to be sedated and put on a ventilator as he could not continue to breathe on his own and had fallen into a coma. A lovely metabolic doctor named Joy came and sat me down to clearly explain what was going on. The metabolic team had cared for another

little girl a year and a half earlier with the same disease. Joy explained to me that Zeke was extremely sick and that he could also die. He had been having seizures and his brain had started to swell. There was no beating about the bush at all - it was straight to the point. My heart was breaking in two. My little boy was all wired up and so helpless and I was all alone. Corey had been in the truck working that day and couldn't get home in time to see his baby boy before we left. I felt so sad for him as he had no idea what was going on and I didn't know whether he would see his little man again.

I was sent to an emergency accommodation room just around the corner from Zeke's ward to try to get some sleep. I cried and cried and cried. I felt useless. I didn't know what to do. I hadn't told anyone this because I wanted to be strong as I was all he had at the specific moment but now I know that it's ok. I am allowed to cry for my baby. It was a difficult time.

About 45 minutes later I was called back to his room. When I got there they were wheeling Zeke out of his room to the Intensive Care Unit. They told me that Zeke had to be put straight onto dialysis. The amount of protein he had gotten



(Zeke cont. on page 16)

(Zeke cont. from page 15)

from my breast milk was killing him!! They said that on a typical test for MSUD leucine levels do not exceed 2000 but in Zeke's case they were well over, the highest they had ever seen!!

It usually takes about 12 hours for dialysis to clear the blood of toxins, but Zeke was on dialysis for 4 days. After 3 days, the nurses reduced the amount of morphine and other sedatives that he was on to see if he would wake up. The next day they took Zeke off the ventilator and later that day he started to come to. He was opening his eyes every now and again and moving his arms up and down. By the next day he was starting to become fully awake for a few minutes each time. It was amazing. He looked like he was growing stronger and stronger each day.

A week after he was admitted, he was doing excellent. He had been taken off all pain killers, the central line from the dialysis was removed and two of his drips had been taken out so he only had one left. I was finally allowed to give my baby a cuddle. After 7 whole days without even being able to touch him I now got to hold him and kiss him. It was the best day ever. Just what I needed.

On the 23rd Of December Zeke was transferred back to our home hospital so we could get to know the pediatrician and nurses. We were all set to go home Christmas Eve which was so awesome after so long away from home when the doctor told me that Zeke had picked up a urine infection from the catheters and needed to stay for another 5 days on IV antibiotics. By now Zeke had had needles in just about every part of his body and most of his veins had seized up so they had to put a drip into a vein in his head. It was terrible for me, but it did not seem to faze him much.

We didn't make it home for Christmas which was horrible. Just Zeke and me in an empty room with no real Christmas spirit as it had been a massive emotional few weeks. A Christmas to forget but also one I'll always remember.

On the 28th of December we were finally allowed to go home!!! We soon got into a pretty great routine. It started off as 3 hourly feeds, which meant absolutely no sleep!! For the first few weeks it was endless amounts of blood tests and urine tests until we settled into 4 hourly feeds and blood tests once a week. As the days went on, Zeke became healthier and happier and just seemed like a normal baby.

All was going great until we had a power shortage on January 15th. Zeke was running out of formula, which we could only get through special prescriptions sent to the chemist. There was massive flooding so the post truck could not get through with the orders. We were pretty much stuffed!! After a lot of



running around trying to sort something out with no power, phone service or way in or out I went to the hospital where a helicopter took us to Melbourne!! Boy was that an awesome trip!! I felt so special. A helicopter ride to Melbourne just to get formula!

On March 11th the doctors called to tell me his blood test results were way too high again. I tried to bring his levels down by using a protein-free formula, but this did not work. We were back in hospital again. After four days on antibiotics he was finally responding well to treatment and we were expecting to go home and then boom. He got gastroenteritis! He was quickly transferred into an isolation room, which was terrible. There was no one there for me to talk to and I could hardly leave the room to stretch my legs as the nurses had their other rooms to attend to. It could be 2 hours before I saw anyone. 3 days later and once again Zeke is finally getting better AGAIN!!! He still has pretty bad diarrhea but stopped vomiting. I was told that Zeke had Salmonella poisoning! I was gob smacked as I didn't know how a little baby who eats no food could have caught this. The doctors had been avoiding me and re directing questions when I asked. Was all a bit suspicious to me and to this day I still don't know how he caught it.

We were no sooner discharged when Zeke began vomiting again. His levels had gone up way too high again. It was another week in the hospital before he was taken off the nasogastric tube and we were set to go home!

In September we were back in hospital again!!! This time Zeke had bronchitis and wouldn't feed. He had his protein-free unwell formula through the NG tube. Although this was not the sickest Zeke had been, he stayed until he was

(Zeke cont. on page 17)



## CAN ADIPOSE ORGAN (FAT) TRANSPLANT BE AN EFFECTIVE TREATMENT FOR MSUD?

By Dr. Christopher Lynch

Recent studies ongoing in Pennsylvania have explored the use of liver transplant for treatment of MSUD. Currently over thirty patients who have undergone this experimental treatment are being studied as part of an exciting project with the Clinic for Special Children in Strasburg, PA and transplant surgeons at the University of Pittsburgh. This procedure greatly lowers the branched chain amino and keto acids (BCAAs and BCKAs) that are elevated in MSUD. Despite excitement about this operation, it is recognized that liver transplant is quite expensive, with first year costs typically over half a million dollars according to a non-profit group, Transplantliving.org (<http://www.transplantliving.org/beforethetransplant/finance/costs.aspx>). There are also the problems associated with competing for a limited pool of donated livers in the U.S.

To try to overcome cost and donor issues, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), a branch of the NIH which covers MSUD research, has funded an exploratory project called an R21 at the laboratory of Dr. Christopher Lynch at Penn State College of Medicine (<http://chrislynchlab.wordpress.com/>) to examine the feasibility of using adipose organ transplant as a source of metabolic capacity for those with MSUD.

Dr. Christopher Lynch and his colleagues have previously studied BCAA metabolism and its role in nutrient signaling as it relates to obesity and diabetes. For example, the BCAA leucine is a nutrient signal that activates signals between cells that growth hormones also use to communicate with tissues. In obesity, BCAAs are slightly elevated and appear to predict the advancement of insulin resistance to Type II diabetes. Dr. Lynch's lab was recognized recently for discovering the high metabolic capacity of fat for BCAA metabolism in humans and rodents. They also recently teamed with a UCLA group to identify the gene that encodes the protein (BCKD phosphatase, gene name: PP2CM) that regulates branched chain ketoacid dehydrogenase (BCKD), the enzyme whose subunits are mutated in MSUD. A genetically engineered mouse missing PP2CM has an intermittent form of MSUD. Another "knock-out" (KO) mouse in Dr. Lynch's lab is missing the enzyme required for the first step in BCAA metabolism. These mice have very high circulating BCAAs, but in contrast to MSUD, low BCKAs. The availability of that mouse is allowing Dr. Lynch's lab to tease apart the contribution of BCAAs vs BCKAs to cellular neurotoxicity in MSUD. Their laboratory has sensitive assays for the BCKAs, which are a better measure of the intracellular concentration of BCAAs. They recently contributed these assays to Dr. Kevin Strauss for his team's studies on the MSUD-liver transplant subjects mentioned earlier.

When we transplanted a very small amount of fat from a wildtype mouse (without the genetic defect) into a mouse lacking the BCATm KO mouse, BCAA concentrations were reduced substantially a few weeks after the operation. For this new project we are trying to improve upon this success. Different kinds of fat are being used for transplant. We are also experimenting with different transplant locations and using different mouse models for the transplant studies including the

PP2Cm knock out (KO) and a mouse created by Dr. Gregg Homanics (University of Pittsburgh), that has a defective E1 subunit with a partial liver rescue (<http://jaxmice.jax.org/strain/006999.html>). (*Editor's note: The development of these mice was supported by the MSUD Family Support Group.*) These different animals each have their own strengths and weaknesses as models for this disease.

In our first study, a collaborative effort with Harvard-Beth Israel Deaconess scientists, adipose tissue was simply transplanted into BCATm knock-out mice. We published this study in the Journal of Biological Chemistry. However animals and humans have "set points" for the weight of their adipose tissues. Transplanting fat by itself causes the transplanted fat and other fat in the animal to shrink to come back to the original weight of adipose tissue before the transplant. In these new experiments we are taking fat out of the MSUD models and then replacing it with "wildtype" fat. We hope this will help the transplanted adipose tissue to survive and hypothesize that the high circulating BCAA/BCKAs in the MSUD models will activate BCAA metabolism in the transplanted fat. These types of operations are difficult in fragile mice, which are about the size of your first two fingers put together. Special micro surgical expertise is needed that is being provided by a research veterinarian who specializes in laboratory animal medicine, Heather Zimmerman, D.V.M.

The type of grant we received is small and short term, reserved for risky but potentially high gain projects. If successful, there are several potential benefits including a larger pool of potential donors and lower costs. First of all it should be far easier to find fat donors than liver donors as fat transplant does not need to be associated with the unfortunate demise of another person to obtain the tissue and the sad feelings that go along with that. In addition, new procedures are being researched in the obesity field right now to try to turn regular fat into another kind of "healthier" fat called brown fat. Brown fat is so named because it is rich in mitochondria, a brown colored organelle of cells. Mitochondria are where the proteins mutated in MSUD are found. Using brown fat should even further increase the amount of BCAA metabolizing capacity of the transplanted fat. Adipose

(Adipose cont. on page 18)

## Preimplantation Genetic Diagnosis (PGD) Can Help MSUD Carriers to Have Healthy Children!

When both members of a couple are carriers of a MSUD mutation, there is a 1 in 4 chance that any child they have will be affected with MSUD, and a 1 in 2 chance that the child will be a carrier. New reproductive technology called Preimplantation Genetic Diagnosis (PGD) can help parents dramatically improve their odds of giving birth to a healthy child.

PGD is an IVF procedure in which embryos are genetically tested before implantation into the uterus, allowing the selection and transfer of unaffected embryos which do not have the specific genetic condition of concern. Reproductive Biology Associates (RBA) offers PGD for individuals and families who are carriers of MSUD, or who have a history of MSUD, as well as for patients of advanced maternal age, or histories of other single gene disorders.

PGD offers a couple an alternative to agonizing over prenatal diagnosis is made following amniocentesis or chorionic villus sampling (CVS) at later stages of gestation. Since PGD is not

100% reliable and only tests for specific defects, parents should consider other prenatal genetic tests, such as amniocentesis or CVS, to confirm results.

RBA has locations in Atlanta, Alpharetta, Lawrenceville, and Fayetteville, GA. We see patients from all over the country and even from all over the world. For out-of-town patients, much of the pre-screening process can be done from your home town. To learn more about PGD and whether this might be an appropriate option for your family, contact RBA at 1-404-257-1900, or visit our website at <http://rba-online.com>. ■

**Jamie K. Dokson, MS, CGC**, Certified Genetic Counselor / Reproductive Biology Associates  
jamie.dokson@rba-online.com

*Editor's Note: Publication of this article does not constitute an endorsement of the procedure by the MSUD Family Support Group.*

(Zeke cont. from page 16)

bottle feeding again and was back to his happy self!! On day four we got to go home :) always the best news to hear!!!

November was the last time we were in hospital for a short stay of only 3 days, not too bad. Zeke had caught another bug and stopped feeding. Corey and I had separated and I was now a single Mum. I had Jacob, now 4 years old, with me as well which was tough but just another hurdle you have to deal. It makes you a stronger person and better parent living with both little lives in your hands 24/7.

I pray he won't have to go back to hospital but I know it's wishful thinking. For now he is healthy and happy and living a great life with his big brother Jacob and me :) xoxo

### WHAT'S IN STORE FOR THE FUTURE

When Zeke is old enough he will be able to live a normal life. Yes, he might not be able to eat the same food, but he can still run and play games and be a kid just like everyone else. ■

(Adipose cont. from page 17)

tissue transplant is already performed in humans by plastic surgeons. Fat transplant operations for cosmetic tissue repair are up to twenty times less expensive than a liver transplant. Adipose tissue is highly amenable to transplant because it has a low oxygen requirement. In addition, implanted adipose tissue attracts nearby blood vessels to form its own blood supply over time in a process called angiogenesis. This means the operation does not require a vascular surgeon. This further contributes to the speed of the operation and lowers the cost. Adipose tissue can also be grown outside the body from cells called pre-adipocytes obtained from a person's adipose tissue. To avoid any rejection issues, it may be possible in the future to obtain these cells from a patient with MSUD, genetically engineer those cells with an un-mutated gene for the E1 or E2 subunit of BCKD, and begin to reintroduce that adipose tissue or the pre-adipocytes back into the patient over time. The first results from these studies should be available in about a year and a half. ■

**Dr. Christopher Lynch** heads a project aimed at exploring adipose tissue transplant for MSUD

**Dr. Christine Olson** is a biochemist who has been developing sensitive new assays to measure branched chain keto acids (BCKAs) for transplant studies. BCKAs are more sensitive markers of tissue concentrations of the BCAAs, where damage occurs when BCAAs are elevated.

**Dr. Heather Zimmerman (D.V.M.)** is a veterinary surgeon working on the MSUD adipose tissue transplant project.



## A Few Words From the Editor

Karen Dolins, EdD, RD, CDN  
Newsletter Editor

I am eagerly awaiting our June symposium. It is thrilling to see how much is happening in the research arena which holds promise for improving the lives of our families! This newsletter highlights just a bit of what we'll be learning about, and shows how researchers have begun to focus on the way that MSUD impacts the brain. The hope is that with this understanding will come ways to prevent high levels of leucine and its keto-acid from causing the damage it does.

As we learn of new families joining our community, it's always helpful to look at those who have managed their disease and are living rich and rewarding lives. We do have so much to be thankful for. I continue to hope that more of you will choose to share your stories as an inspiration to others. Sadly, we also share with you the life story of Britney Page, classic MSUD, who died at the age of 18.

I'd like to thank Michael Koons and Lindsey Miller for volunteering to help with the newsletter and for the contributions they've made to this issue.

As our facebook page shows, we get so much strength from each other. This is never more powerful than when we are together at symposium. I hope that many of you will be there so that we can continue to learn from and support each other.

With warmth,  
Karen Dolins  
Mom to Hannah, 17, classic MSUD



## Amy Jones, Board Member

Mom to Derek, Classic MSUD almost 10

I would like to introduce myself and my family to the MSUD community. My name is Amy Jones and I have been asked to be the newest member of the MSUD board.

This is an honor that I never expected. This is a group of people that have done more for my family than I could have ever imagined when we were introduced to this world of MSUD almost 10 years ago. While we are on the subject, please let me introduce you to my family.....

My husband Dean and I have been married for almost 11 years now (May 12, 2001). On April 12, 2002, we welcomed our first baby boy, Derek Lawrence, into the world. Almost 2 years later, we had our second little boy, Adam Thomas, born on February 1, 2004. But it was Derek who we will talk about here. At first, he was perfect! But after a few days, he became very, very fussy, he stopped feeding, he would not sleep for more than about 10 minutes at a time and he never really opened his eyes. As a first time mom, I wasn't sure what I was doing wrong or where to go or who to ask. And then I got a phone call from our pediatrician's office telling us that although they were quite certain that it was a lab error, we were to be looking out for some really strange symptoms and behaviors with Derek. They were going to re-test him in the meantime, but to be cautious anyway. As many of you know, we thought they were crazy. After 2 more days, they called back and confirmed that the bloodwork showed that Derek had this incredibly rare metabolic disorder called Maple Syrup Urine Disease and that we needed to get him to our hospital here in Akron, OH ASAP because they believed that since he was now 12 days old, the disease could be causing some brain and kidney damage.

After being in the hospital for a few hours, he was transferred to University Hospitals in Cleveland (Rainbow Babies and Children's Hospital) where he spent the next 2 weeks. That is where we met the doctors that saved his life, not just that once, but many times since then. We as a family have decided that we cannot just sit by and let this disease run our lives. We have put together over the last 6 or 7 years several different types of fundraisers. All of the proceeds that we raise go directly to the support group to be used in whatever way is needed to help find a cure. The most profitable fundraiser that we do is a Night at the Races. We have been able to raise and donate over \$30,000 within our family and our small community here in Barberton, OH. We make sure that Derek is there every year so that the people who are attending can see the progress that he is making and they can put a face to the cause.

Derek is now almost 10 years old. He plays soccer and basketball. Although he has to deal with the everyday struggles of MSUD, with the support that we have from not only our community here in town but also from our MSUD Family Support Group at the symposiums and more, we believe that we will be able to cure this disease someday and help all of those affected!

Dean, Amy, Derek and Adam Jones

# MSUD Symposium 2012

Mark your calendars!

## June 28-30

at the Embassy Suites- Airport  
Philadelphia, Pennsylvania

See pages 4 and 5 for more info

**Organizational Contacts**

Contact for general information:  
**Kay Larsen**, Easton, Pennsylvania  
 610-252-8572 • kaysfo@aol.com

Contact for organizational information  
 & printed material:  
**Sandy Bulcher**, *Director* • Powell, Ohio  
 614-389-2739 • dbulcher@aol.com

Contact to be added to the mailing list or  
 make a donation:  
**Dave Bulcher**, *Treasurer* • Powell, Ohio  
 614-389-2739 • djbulcher@aol.com

Contact for legislative & educational issues  
**Marcia Hubbard**, *Corresponding Sec.*  
 Cedar Hill, Missouri  
 636-274-2021  
 wingman90gl1500@juno.com

Contact for inquiries in Spanish  
**Monica Falconer**, *Spanish Contact*  
 Anchorage, Alaska  
 907-770-6065 (Alaska time zone)  
 monicazf@yahoo.com

Newsletter Editor  
**Karen R. Dolins, EdD, RD**  
 33 Valley Road, Scarsdale, New York 10583  
 914-723-5458 • krdhed@aol.com

**Medical Advisors**

**Holmes Morton, M.D.**  
 Clinic for Special Children, Inc.  
 535 Bunker Hill Road  
 P.O. Box 128, Strasburg, PA 17579  
 717-687-9407 / Fax: 717-687-9237  
 Clinic Website:  
 www.clinicforspecialchildren.org

**Susan C. Winter, MD**  
 Dir., Med. Genetics/Metabolism  
 Valley Children's Hospital  
 9300 Valley Children's Place  
 Madera, CA 93638  
 559-353-6400 / Fax: 559-353-7213  
 winter2571@aol.com

**Neil R. M. Buist, MD**  
 Professor Emeritus  
 Pediatrics and Medical Genetics  
 Oregon Health & Science University  
 buistnrm@aol.com

**Melissa Wasserstein, MD**  
 Dir., Program for Inherited Metabolic  
 Diseases  
 Associate Professor  
 Dept. of Genetics and Genomic Sciences  
 Mount Sinai School of Medicine  
 New York, NY 10029  
 212-241-2478 • Fax: 212-860-3316



**Nutritional Advisors**

**Rani Singh, Ph.D., R.D.**  
 Emory University  
 Div. of Medical Genetics  
 2040 Ridgewood Dr.  
 Atlanta, GA 30322  
 404-727-2866 / Fax: 404-727-5783  
 rsingh@genetics.emory.edu

**Sandy van Calcar, M.S., RD**  
 University of Wisconsin  
 Biochemical Genetics Clinic  
 1500 Highland Ave.  
 Madison, WI 53705  
 608-263-5981  
 vancalcar@waisman.wisc.edu

MSUD Family  
 Support Group Board

Wayne Brubacher, *President*  
 (Indiana) 574.862.2992

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