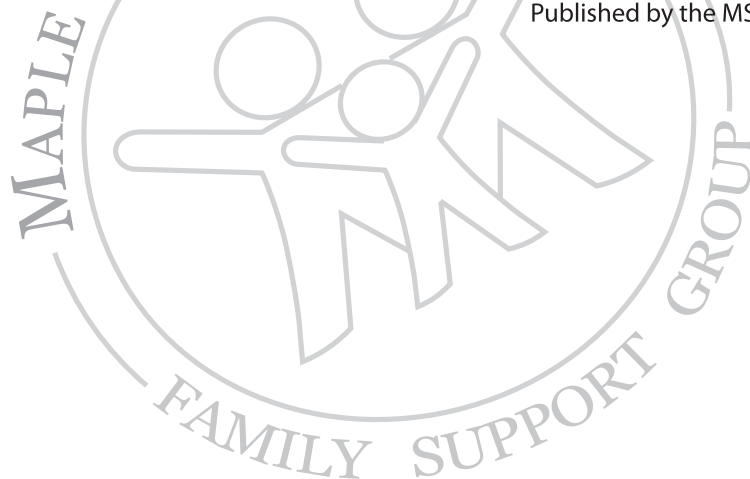


MSUD NEWSLETTER

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MSUD SYMPOSIUM 2012



Sandy Bulcher, Director and Symposium Chair

MSUD Symposium 2012 was held at the Embassy Suites-Airport in Philadelphia, PA on June 28th -30th. . The 280 people attended the three day event included families from 22 of the 50 United States, Canada, Mexico, United Arab Emirates, Australia, Italy, and United Kingdom. Included were 69 individuals with MSUD ranging in age from 6 weeks to 44 years, along with 10 who had undergone liver transplantation.

A reception was held Thursday evening in the beautiful atrium of the Embassy Suites. During that time, families enjoyed renewing old friendships and meeting new families. For the first time, attendees also had an opportunity to purchase T shirts with the MSUD logo. Thanks to Dean and Amy Jones for making that possible.

Friday was a full day of speakers, including many research updates. Dr. Holmes Morton was first to speak and he enlightened us on the topic of the treatment of MSUD from 1986-2012. Following Dr. Morton, Dr. George Mazariegos educated the audience about what they need to know when considering a liver transplant. Next, Dr. Brendan Lee discussed the possibility of treating MSUD with Phenyl butyrate. Just before lunch, David Fischler, MSUD adult from Georgia, shared about his life with MSUD. A summary of their sessions are

(Symposium cont. on page 2)

Progress Toward Evidence-Based Nutritional Management Guidelines for MSUD

Dianne Frazier, PhD, MPH, RD

Professor emeritus

Department of Pediatrics, Division of Genetic and Metabolism

University of North Carolina, Chapel Hill NC

As was presented at the MSUD Symposium in June, the Nutrition Management Guidelines for MSUD are nearing completion. This project, described in the Fall 2010 MSUD Family Support Group Newsletter, is a collaboration between the Southeast Regional Collaborative (SERC) with funding from the Health Services Research Association (HRSA), and the Genetic Metabolic Dietitians International (GMDI) and aims to prepare guidelines for a number of inborn errors of metabolism treated through dietary intervention. The GMDI guideline workgroups are

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included in this issue of the newsletter.

The afternoon began with Susan Hutson PhD explaining what she has learned from the mouse model, and how that may help guide future treatment. Kristin Skvorak PhD then shared information about her work treating MSUD mice with hepatocyte transplants. The afternoon ended with Emilie Muelly PhD discussing her studies on the neurochemical and neurocognitive effects of MSUD. During the breaks, families and professionals had an opportunity to visit the vendors that participated in the conference, including Nutricia North America, Vitaflo, Applied Nutrition and Children's Hospital of Pittsburgh of UPMC. The day concluded with a group photo of those with MSUD. It was challenging to get over 60 MSUD children and adults to stand still while many people took pictures, but it was very worthwhile and reminded us that we are a family. After dinner, some families enjoyed visiting with each other at the hotel, while others went into Philadelphia for dinner and sightseeing.

Saturday morning began with Dianne Frazier PhD, RD educating us about the guidelines for nutritional management that are being developed. Next, Dr. Ira Fox shared his knowledge of hepatocyte transplantation for the treatment of metabolic diseases, which was followed by Dr. William Zinnanti's presentation on his work with the MSUD mice. Gerald Downes PhD then shared how zebrafish could be used as an animal model for MSUD. Finally, Dr. Mario Cabrera-Salazar discussed gene therapy as a potential option for treating MSUD.

Following lunch, we played a fun and educational game of trivia which tested the MSUD knowledge of nine young adults. We then watched a DVD of the show "Mystery Diagnosis," which aired in 2010. It featured the Webb family from NC and highlighted their struggles until their daughter, Rachel, was finally diagnosed with MSUD. Libby Stone then shared her vision of an adult MSUD group. The day concluded with discussions about the website, newsletter, and an update from the MSUD Board.

Special thanks to United Service Foundation for their generous donation, which allowed many MSUD families to attend the symposium. Also, thanks to our sponsors: Applied Nutrition, Children's Hospital of Pittsburgh of UPMC, Mead Johnson, Charles, Hehmeyer, Scott C. Foster Metabolic Fund, and Vitaflo. Finally, we were able to provide low protein meals throughout the weekend due to the generous donations of Applied Nutrition, Cambrooke Foods, PKU Perspectives, Taste Connections, and Brenda Wenger.

The event would not have been possible without the assistance of the MSUD Symposium 2012 committee members, which included Wayne and Joyce Brubacher, Denise Langosch, Barbara Mudrick, and Julie Szymczak.

Watch for the date and location of MSUD Symposium 2014 in future newsletters and the MSUD website (www.msud-support.org) Hope to see you there! ■



A Few Words From the Editor

Karen Dolins, EdD, RD, CDN
Newsletter Editor

A Message from the Editor

It's always a treat to produce a newsletter following a symposium, as there's so much information to share with those of you who were unable to attend. This time around it is particularly rewarding as there is so much exciting research to report on.

In this issue you will find summaries written by our speakers. In some instances I have written summaries which I sent to the speakers for review and approval. As a prelude to the symposium, we learned about the work of other speakers in our Winter/Spring 2012 issue. Please refer to that issue to hear about Dr. Downes' work with MSUD zebrafish, Dr. Lee's preparation for a clinical trial with Buphenyl, and Dr. Hutson's ongoing work with MSUD mice.

In addition to these research reports, I'm sure you will enjoy reading about Laurie Guthrie of Scotland and her amazing accomplishments writing, directing, and acting in her first professional play. In our MSUD Milestones section we learn of Brittany Fuller's marriage and Jordan Bulcher's college graduation and acceptance into graduate school. We continue to enjoy and benefit from Glenda Groff's recipes. In this issue we also hear from a new MSUD mother, Dana White, mom to Charlotte age 1 transplanted, who happens to be a registered dietitian with a specialty in recipe development. Dana has contributed recipes using seasonal ingredients.

So dig in, enjoy, and I hope you will contribute to future newsletters. Family stories and milestones are always read with interest.

Warmly,
Karen Dolins

Mom to Hannah, age 18, Classic MSUD

ENJOY READING OUR MEMBER'S STORIES?

WE'D ENJOY READING YOURS!

Contact the editor: Karen R. Dolins- krdhed@aol.com

Tip from Genetic Alliance

Traveling can be a stressful time for someone with a disability. The Transportation Security Administration (TSA) has a new toll-free hotline, 855-787-2227, to provide information for passengers with disabilities and medical conditions and their families before they fly. They recommend calling 72 hours in advance to learn what to expect at security checkpoints. They will also be able to coordinate your security screening ahead of time when they know about your disability. This is a great resource for families traveling with a child with a disability. You can plan in advance, and know exactly what to expect at specific airports.



Jordan Bulcher, age 22 (Classic MSUD), graduated from The Ohio State University in the spring of 2012 with a degree in Molecular Genetics. In June 2012, he started at Marietta College in the Physician Assistant Program.

(*Dr.Frazier* cont. from page 1)

using a well-designed and referenced method of evaluating articles published in scientific journals, protocols used at various clinics, book chapters, and presentations at scientific and support group meetings. This “evidence” is then ranked according to its scientific merit including study design and use of controls. Further expert opinion from both metabolic physicians and dietitians is gathered using two surveys and a face-to-face meeting known as the nominal group process.

The management guideline for MSUD cannot provide “one-size-fits-all” recommendations: not all mutations of the genes for the enzyme (BCKD) are the same; in addition, there are genetic difference among individuals with MSUD even if they have the same BCKD gene mutation ; and finally, there are differences in access to trained health professionals, biochemical monitoring, and to the medical foods necessary for treatment. Also, existing case studies of patients with MSUD and clinic protocols may lack the scientific rigor needed to be applied to all patients. That is why a process was developed to evaluate each of the documents so that the combined data could be used to form the guidelines. Where there are gaps or widely divergent opinions in the information from these sources, input from experts is used to provide additional insight.

Early in the process of development, the GMDI workgroup agreed on five research questions to investigate and use as the backbone of the MSUD guidelines. These are:

- For the individual with MSUD, what is the most effective method for initiating, dosing and evaluating response to thiamin supplementation?
- For the individual with MSUD, treated through dietary modification, what are BCAA blood levels that lead to optimal nutritional, medical and quality of life outcomes?
- For the woman with MSUD, what specific nutritional interventions must be initiated during pregnancy, at delivery and during the postpartum period to achieve optimal outcomes for her and her newborn infant?

- For the individual with MSUD or suspected MSUD, what nutritional interventions must be initiated during metabolic decompensation, illness, trauma or surgery to achieve optimal outcomes?

- For the individual with MSUD, undergoing liver transplantation what specific nutritional interventions result in optimal nutritional, medical and quality of life outcomes?

One of the findings, when researching information to answer research question #5, was that there was little published data on transition to an unrestricted diet, evaluation of the nutritional adequacy of the new diet, or assessment of biomarkers for nutritional status after a liver transplant. Individuals who had previously obtained most of their calories, vitamins and minerals from their medical food (metabolic formula) may need guidance to meet these nutritional needs from table foods. Also, individuals who have never tried high protein foods may have such an aversion to them that it is difficult to meet their protein requirements. These concerns may not apply to all individuals with MSUD who receive a liver transplant, but the guidelines make recommendations that some nutritional counseling and oversight be made available post-transplant.

Presently, all the evidence for the MSUD guidelines has been gathered and evaluated, and the surveys and the nominal group process has been completed. As part of the guidelines, the GMDI Education Committee has evaluated and annotated appropriate resources for use by patients and providers. The writing of the final document is expected to be completed before the end of 2012. Input from the MSUD community has been an extremely valuable part of the process.

Evidence analysis in the preparation of guidelines allows evaluation of current practices and points the way to future research studies. Completed guidelines help standardize treatment strategies and provide consistency in care. They also provide information to support coverage by third party reimbursers. They will be available electronically and updated on a regular basis. ■

Perseverance

By William Zinnanti, M.D., Ph.D.

It was great to have the opportunity to present my research work at the biannual MSUD support group meeting in Philadelphia. I enjoyed meeting so many families from all over. It is tremendously important as a researcher to have this opportunity to meet the families and patients with MSUD. This reminds us like no other opportunity, who we have the chance to help with our work. Hearing the stories of troubles and perseverance from the families is amazing.

My trip to the meeting in Philadelphia was quite a challenge. It all started on the day I was to leave when the airline called to let me know my flight was cancelled but I could have one the next day. That would not work as I would miss the meeting, so I went to the airport early and argued my way on to another flight to Washington DC with a connection to Philadelphia. Since the flight was delayed, I did not have much hope of meeting my connection in Washington DC. When I arrived, though, all flights were delayed due to storms in the area so I thought I might be able to catch the connection. After waiting for a couple of hours, I was told that the flight was cancelled. At midnight, I rented a car and headed to Philadelphia. The roads were a disaster because of the weather that caused the flights to be cancelled in the first place. There were huge trees lying across the freeway and some cars had already run into them. I made my way out of Washington DC and up to Philadelphia arriving around 3 AM. I had to be there.

This one difficult trip is no comparison to the days and nights that patients and their families have spent in the hospital hoping and praying for answers and recovery. The constant challenges of staying well and making the right choices to stay healthy can be extremely challenging. This brings me to my current challenge. I seek to find novel and available treatments that can prevent MSUD coma and potentially loosen dietary constraints without risking the health of the brain. For this purpose, Dr. Kristen Skvorak has provided me with MSUD mice at Stanford so that I can test norleucine and gabapentin and their ability to prevent rapid accumulation of leucine and keto-isocaproic acid in the brain. These tests are being conducted with MSUD mice to make sure these drugs are safe before making them available for patients. We have our challenges because we have to breed a lot of mice for these tests, but we will persevere. We have already conducted the first few experiments on gabapentin and are awaiting results. Much background work has been completed in order to detect if we are achieving our goal. This is the main focus of my work, and I hope to have some results to report in the next couple of months.

Thank you to all MSUD patients and families that share their stories and inspire us. ■



Cindy Blau, age 52 with Classic MSUD from Columbus, Ohio visited New York City in June 2012 with her friend Jimmy. (She is SO excited to get her picture in the newsletter!)



Submitted by **Dana White**, mom to **Charlie**, 1 year, transplanted

Strawberry Granita Serves: 6

You can make this recipe using any kind of berries or stone fruit – raspberries and peaches are also delicious.

4 cups water
Juice of 1/2 lemon
1 pint strawberries, finely chopped
1 cup sugar

Combine water, lemon juice, strawberries and sugar into a large saucepan. Bring to a boil; reduce heat to medium and cook for 5 to 7 minutes until berries have broken down. Strain mixture through a fine mesh strainer (use a rubber spatula to press through). Transfer to a shallow glass container (such as a 9x13x2 inch baking dish); allow to cool slightly, then place in the freezer. Once the mixture begins to freeze, scrape with a fork to create ice crystals every 30 minutes until mixture is completely frozen. To serve, spoon out into bowls or paper cones.

Nutrition Info Per Serving

Calories: 146 / Total Fat: 0 grms / Saturated Fat: 0 grams
Total Carbohydrate: 37 grams / Sugars: 36 grams
Protein: 0 grams (Leucine: 0.02g; Isoleucine: 0.01g; Valine: 0.01g)
Sodium: 7 milligrams / Cholesterol: 0 milligrams
Fiber: 1 gram

A Second Chance at Life

Brittany Fuller

Age 24 Transplanted Feb. 2006

Many of us MSUD kids have always wondered what it would be like to live without this disease. I was one of those kids growing up. When would I be able to have chicken, ice cream or even chocolate? As the years rolled by no treatment was ever available until I learned about the option of a liver transplantation during a symposium in 2004. This would change my life forever. Unfortunately my parents didn't see the importance of me receiving a new liver at that point in time.

Two weeks after I was born on September 1987, my parents found out that I had this disease called Maple Syrup Urine Disease or MSUD. They had never heard of this disease before and were fearful of the damage it could cause me if not treated properly. We lived in Baltimore, Maryland, and I was treated at Johns Hopkins Hospital. My parents learned all they could about it, with the help of our metabolic doctors, in order to keep me alive and healthy. After all that they had learned from the doctors, I was able to go home and live a normal life under a restricted diet.

We moved to Columbus, Indiana when I was 5, and I did well. After years of learning how to manage my diet and monitoring it along with my parents monitoring, things started to change during my junior year of high school. My leucine levels would jump all around and we were having a hard time keeping them under control. I remember one day after getting into a fender bender I found that my leucine levels were off.

A PERSONAL STORY

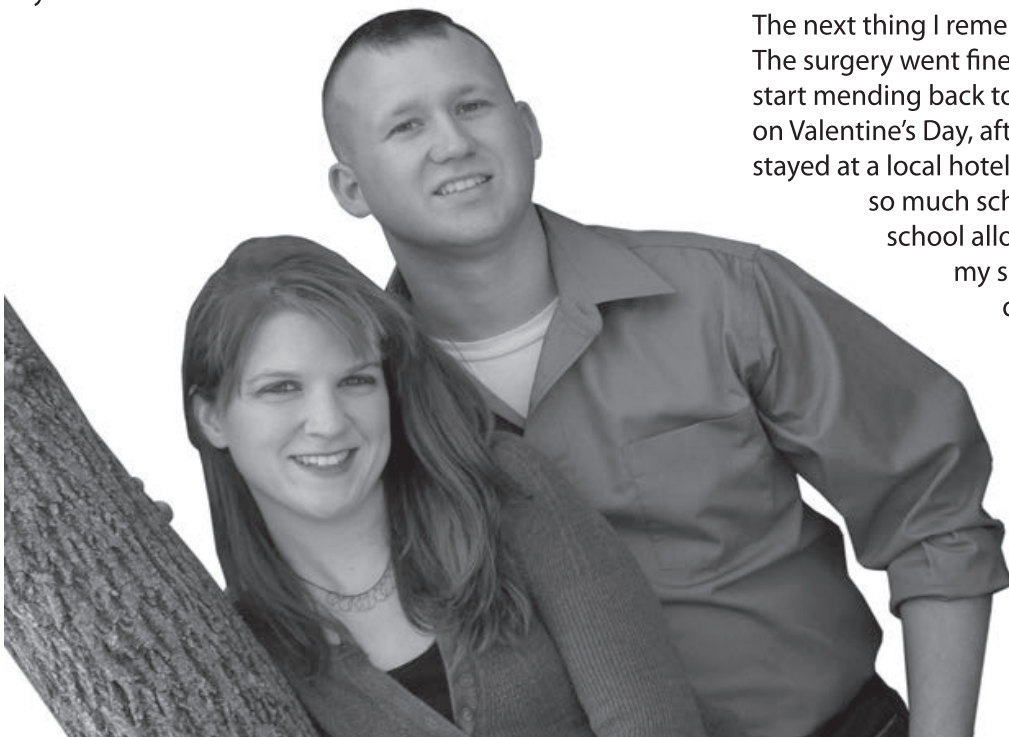
We realized that when my levels were off my mind wasn't focused enough to drive. So every morning I had to check my DNPH levels before I was allowed to drive to school. One day they would be fine and then the very next day they would be off. It was very frustrating for me because my levels were out of whack and I didn't know what was causing it. We didn't change any of my formula ingredients or my diet limits.

After my last stay in the hospital, my doctor at Riley Children's Hospital in Indianapolis, Indiana, asked if my parents and I ever considered a liver transplant. I had always wanted a "cure" for this disease but my parents felt differently and had said no before. After hearing that my doctor thought it might be a good idea, my parents started considering it and contacted the liver transplant coordinator over in Pittsburgh Children's Hospital to schedule an evaluation.

After going through the evaluation, doctors told me that I was a good candidate and I went on the waiting list for a liver in October 2005. After only two months on the waiting list, I received "the call" but found out when we got there that I was a back up to a girl that needed five organs transplanted at once and wasn't going to be getting a liver at that time. We went home and waited some more for that special call. I tried to go on with life as normal as possible but the waiting part of the game was the hardest thing I had to do. Finally on February 1, 2006 I received the call at 2am. We got to the Pittsburgh hospital in 6 hours and waited all day to receive word. At 9pm February 2nd, we got the okay to go through with it. I was prepped for surgery, taken into the OR and on February 3, 2006 I had my new liver.

The next thing I remember was waking up to see my parents. The surgery went fine and all I needed to do was recover and start mending back together. I was released from the hospital on Valentine's Day, after having constant good results, and stayed at a local hotel for the next couple of weeks. I missed so much school while I was there but thankfully my school allowed me to correspond by mail. It was my senior year of high school, and I was determined to graduate on time despite being in the hospital for most of the semester. After a month away from home, my parents and I were able to finally go home and only return to Pittsburgh for clinic visits. It was the middle of flu season, so I was restricted to home for another couple of weeks before I was fully able to return to school.

(Brittany cont on page 7)





Gene Therapy for Maple Syrup Urine Disease - Realities and Challenges

Mario A. Cabrera-Salazar MD.
Rare Diseases Science
Genzyme Corporation, a Division of Sanofi,
Framingham MA

The existence of many genetic conditions, most of them with unmet medical needs, has prompted interest in the development of alternatives that may constitute definitive treatments for these conditions, or at least substantially reduce their symptoms. Maple Syrup Urine Disease (MSUD) and other metabolic diseases may be candidates for gene therapy approaches. However, successful implementation of gene therapy for metabolic diseases depends on overcoming significant current technical and scientific challenges.

Gene therapy modalities:

The main gene therapy approaches are *in vivo* and *ex vivo* modalities. *In vivo* gene therapy directly delivers the gene to the patient or takes advantage of the ability of viruses to deliver genes into the cells. *Ex vivo* gene therapy requires removing cells from the patient, correcting the genetic deficiency by gene delivery in cell culture and then returning the corrected cells to the patient. For safety, the viruses used for gene therapy are rendered incapable of replicating or causing disease but retain their ability to deliver a gene to the target cell for the subsequent production of a (missing) protein.

Why develop gene therapy for neurometabolic diseases?

Neurometabolic diseases such as MSUD are caused by mutations in a single gene that result in the absence of a protein required to transform substances for the normal functioning of the body. In classic MSUD, the inactivity of a protein known as the E2 subunit of the Branched Chain Ketoacid Decarboxylase (BCAD) disrupts the metabolism of the amino acid leucine, leading to its accumulation throughout the body with resultant toxicity. Gene therapy experiments in mouse models of a group of diseases known as lysosomal storage disorders (LSDs), as well as those in the metabolic disease phenylketonuria (PKU), have provided valuable insights of how gene therapy might be used for MSUD as well as some of the challenges associated with a gene therapy approach.

For example, it has been shown in mouse models of Pompe disease (an LSD in which a deficient enzyme causes accumulation of a specific sugar in muscle and heart leading to disability and death) that it may not be necessary to correct all of the cells in an organism to have satisfactory results. Thus, in gene

therapy experiments in a Pompe mouse, disease symptoms can be treated by correcting the metabolic defect in a portion of the liver using an adeno-associated virus to deliver the normal gene. This corrected cell mass produces and exports the missing enzyme (metabolic cooperation) which is then taken up by all the muscles, reducing their stored sugar and abating morbidity (Ziegler et al. 2008).

Is gene therapy feasible for MSUD?

One of the highlights of the presentations at the symposium held on June 28th-30th was that metabolic cooperation is achievable in MSUD by either liver transplant (patients) or hepatocyte (liver cell) transplantation (mouse models). In the mouse experiments, injection and engraftment of a critical mass of hepatocytes (as little as 50,000 cells) allowed the mice to metabolize the excess leucine of the entire body. Based on this result, it would be reasonable to believe that a gene therapy approach that replaces the deficient subunits of the BCAD complex in a portion of the body might also prove beneficial for patients with MSUD.

However, one of the foreseeable challenges for an *in vivo* gene therapy approach in MSUD can be extrapolated from experiments in mouse models of PKU (a disease similar to MSUD in which a liver enzyme, phenylalanine hydroxylase (PAH) is deficient). It was observed in this model that the non-functioning enzyme (which continues to be produced) could inactivate the correct enzyme produced by gene therapy, thus making it more difficult to generate a therapeutic effect (Waters et al. 2001). For PKU this effect can be countered by giving very high doses of the virus (100-1000x that used in Pompe mice) or by targeting the virus to tissues that do not normally express PAH, such as muscle. However, in the case of MSUD, the enzyme deficiency is not limited to the liver but occurs in all tissues of the body, and many copies of the E2 subunits are necessary for the adequate metabolism of leucine (Zinnanti and Lazovic 2012). As observed in the PKU model, the correct E2 subunits produced by gene therapy may associate with the incorrect E2 subunits within the cell and their activity may be decreased or neutralized, thus requiring administration of very high doses of virus.

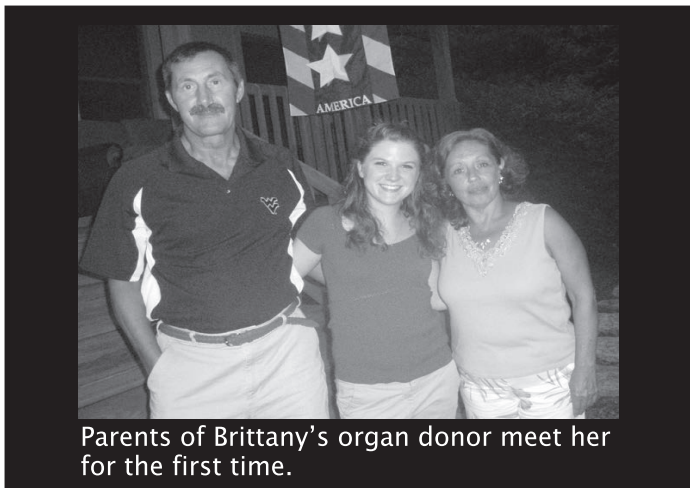
Another significant hurdle for gene therapy using viral vectors is the existence of antibodies (immune molecules) that can recognize and facilitate destruction of the vector in a significant proportion of humans. Studies in monkeys that are naturally exposed to these viruses have shown that it is very difficult to overcome pre-existing antibodies against the virus and thus adds a level of complexity to gene therapy approaches based on these vectors. These anti-vector antibodies are not observed in mouse models due to the environmentally controlled conditions in which they are housed. However, when mice are exposed to the virus they also develop antibodies that can neutralize the viral

(Dr. Cabrera-Salazar cont on page 8)

(Brittany cont from page 5)

After the transplant, life started to change for the good. I graduated from high school and got accepted to Ivy Tech community college so I could stay home for the first year of my "new" life. I felt different from before the surgery. I could see clearly, meaning before this I felt that my vision and mind was always cloudy. But I see things clearly now, I am able to focus more and my family has mentioned that I am the "happy" person that they remember.

During my last year of college in 2010, as I was celebrating my fifth year from having my transplant, I met with my donor family when they were passing through Indiana on their way to Yosemite Park. My donor was a 19 year old girl by the name of Brianna. Her parents Bill and Sue had wanted to contact the recipients of their daughter's organs. I had written them a letter in the beginning thanking them for the gift their daughter gave me and we had been in contact ever since.



Parents of Brittany's organ donor meet her for the first time.

I graduated from Indiana University in 2010 with a Bachelor of Science in Tourism, Convention and Event Management. I didn't know where I wanted to go or what career path I wanted to take. I interned while in school at Walt

Disney World and Cummins Inc. in my home town so I decided to return there. I am still there, working full time and living away from my parent's house, which I would have never thought would happen if I had not went through with the transplant.

When I secured a position at Cummins Inc it was a great thing for me. I was able to be close to home, get my footing on the ground career wise, and I met my future husband, Shawn Richards again. We first met when we were in middle school together and were friends. We grew apart after the middle of 8th grade year when he transferred to another school and we lost contact until May of last year. It was ironic how we met and how it all started. My mother had told me a year before to go on an online dating website to meet someone, and it turned out to be the best thing that ever happened to me. After dating for couple months but remembering when we were friends many years ago, Shawn asked for my parent's blessing to marry me and then asked me on my 24th birthday. We plan to get married September 1, 2012 in front of all our family and friends in our hometown Columbus, IN.

If I would have never had the transplant I don't think I would be where I am now. I live on my own; I bought a house, graduated from college, am getting married, planning to start a family, and starting my own business. The liver transplant has saved my life and brought me things that I want to accomplish in my life. But most of all it bought my parents a clear mind to their everyday lives. Before the transplant, they worried constantly about what would happen to me mentally and physically if I got sick. With the liver transplant, they were able to get their lives back and not worry as much about me, and for this I am grateful. ■

Roasted Vegetable Soup

Makes 8 cups

Submitted by **Dana White**, mom to **Charlie**, 1 year, transplanted
Make roasted veggies as a dinner side dish and turn leftovers into this creamy and delicious soup. Chop everything into similar sized chunks for even cooking. This soup also freezes beautifully. A bit higher in leucine, but nutrient packed!

1 small butternut squash (about 2 pounds), peeled, seeded & diced
1 medium onion, chopped
12-ounces potatoes, peeled and chopped
2 medium carrots, chopped
2 teaspoons fresh thyme leaves
2 tablespoons olive oil
1 teaspoon kosher salt
Freshly ground black pepper to taste
6 cups low-sodium vegetable broth*

Preheat oven to 400-degrees F. Place chopped vegetables and thyme on a large sheet pan. Drizzle with olive oil, season with salt and pepper, and toss well. Roast for 30 to 40 minutes until vegetables are tender. Transfer cooked vegetables to a large soup pot and add vegetable broth. Puree soup in a blender (in batches), or leave in the pot and use an immersion blender. Once pureed, heat over medium heat until warmed through.

Nutrition Info Per Serving

Calories: 126 / Total Fat: 4 grams / Saturated Fat: 1 gram
Total Carbohydrate: 24 grams / Sugars: 6 grams / Protein: 2 grams
(Leucine: 100 mg; Isoleucine: 80 mg; Valine: 90 mg)
Sodium: 575 milligrams / Cholesterol: 0 milligrams / Fiber: 4 grams

*Make your own vegetable broth: combine onions, carrots, celery, garlic cloves, bay leaf and some whole peppercorns in a large stock pot. Add enough water to cover; season with salt. Bring to a boil, reduce to a simmer and cook until reduced by half. Strain and transfer to plastic or glass containers. Store in the refrigerator for up to one week or in the freezer for up to 3 months.

Neurochemical and Neurocognitive Effects of MSUD

Emilie Muelly, PhD

Those of you who read our Winter 2012 issue will be familiar with the fascinating research Dr. Muelly is conducting at Hershey Medical Center in collaboration with the Clinic for Special Children. Symposium attendees had the opportunity to hear her speak in greater detail about her work. Dr. Muelly studied the brain chemistry of MSUD patients, with and without liver transplant, and siblings without MSUD. Of those with MSUD, 29% met criteria for mild mental retardation (score <70) and 17% were in the borderline IQ range (score < 80). Through use of medical records as well as a structured clinical interview, she found that these individuals also had a higher incidence of attention deficit disorder, depression, and anxiety than their siblings. Those with MSUD who were sick at the time of diagnosis had a 10 fold increased risk of becoming depressed and were 5 times as likely to develop an anxiety disorder than those who were diagnosed before going into crisis.

Dr. Muelly explained that amino acids are carried into the brain via chemical transporters. When leucine levels are high, these transporters become flooded with this amino acid and are able to carry fewer of the other amino acids, creating an imbalance of amino acids in the brain. Tyrosine, a precursor for the neurotransmitter dopamine, is one important amino acid thus affected, and may be one explanation for the higher incidence of attention deficit hyperactivity disorder (ADHD) seen in MSUD. Levels of glutamate, another important neurotransmitter, are also affected.

Another theory which may explain the neurocognitive effects of MSUD relates to the high energy requirements of the human brain. The buildup of ketoacids observed when leucine levels are high may impair the brain's ability to produce the amount of energy it needs. N-acetyl-aspartate (NAA) is a brain chemical which can be used to evaluate the energy status of the brain. Higher NAA levels are associated with higher performance IQ, suggesting that the brain needs more energy to perform well. Levels of this brain chemical have been found to be decreased during MSUD crisis. Using Magnetic Resonance Imaging (MRI), Dr. Muelly found abnormal levels of these brain chemicals in MSUD patients even when not in acute crises. She was also able to demonstrate that glutamate levels are low in MSUD patients under control. No differences were observed in patients who had undergone liver transplantation, but she hopes to study this further as several families do report improvement in well-being and various psychiatric symptoms.

Dr. Muelly plans to provide an update on her findings in the next issue of the newsletter. ■

(Dr. Cabrera-Salazar cont from page 6)

gene therapy vector and render it ineffective (Hurlbut et al. 2010).

When can we expect gene therapy to become a feasible approach to genetic disease?

Initiating clinical trials in humans is conditioned on several parameters of safety and efficacy that are evaluated in animal studies. One of the limiting technical problems for clinical trials is the ability to produce enough clinical grade virus for trials and a subsequent approved product. Currently, several research groups are trying to obtain an "ideal virus", that is, one easy to produce, with very high performance and safety profiles and that can overcome the limitations noted above. Until this goal is realized it would be prudent to continue your current treatment plan, strive to live a healthy lifestyle and keep informed through the MSUD family support group of the latest developments and modalities of treatment available.

On a personal note, I enjoyed the opportunity to interact with the MSUD family support group during the symposium and would like to thank all the attendees for the lessons I learned at the meeting. ■

References:

Hurlbut GD, Ziegler RJ, Nietupski JB, Foley JW, Woodworth LA, Meyers E, Bercury SD, Pande NN, Souza DW, Bree MP, Lukason MJ, Marshall J, Cheng SH, Scheule RK. (2010) Preexisting immunity and low expression in primates highlight translational challenges for liver-directed AAV8-mediated gene therapy. *Mol Ther.* 18(11):1983-94

Waters PJ, Scriver CR, Parniak MA. (2001) Homomeric and heteromeric interactions between wild-type and mutant phenylalanine hydroxylase subunits: evaluation of two-hybrid approaches for functional analysis of mutations causing hyperphenylalaninemia. *Mol Genet Metab.* 73(3):230-8.

Ziegler RJ, Bercury SD, Fidler J, Zhao MA, Foley J, Taksir TV, Ryan S, Hodges BL, Scheule RK, Shihabuddin LS, Cheng SH (2008). Ability of adeno-associated virus serotype 8-mediated hepatic expression of acid alpha-glucosidase to correct the biochemical and motor function deficits of presymptomatic and symptomatic Pompe mice. *Hum Gene Ther.* 19(6):609-21

Zinnanti WJ, Lazovic J. (2012) Interrupting the mechanisms of brain injury in a model of maple syrup urine disease encephalopathy. *J Inher Metab Dis.* 35(1):71-9

Why Transplant Families Should Attend MSUD Symposiums: A Perspective from Two Families

Sheryl Leinbach Mom, Louisa age 8, transplanted 2009

I attend MSUD Symposiums even though my daughter had a liver transplant. I cannot lightly walk away from the MSUD Family Support Group because it has so greatly impacted my life. I will always be immensely interested in MSUD, having lived it for 4 years and 10 months with my daughter, expanding every energy to learn all I could, an investment that I find difficult to leave behind. Our experiences with MSUD and liver transplant have shaped my life in lasting ways more than any other thing. The relationships the support group has brought into my life are precious to me. I desire those friendships to continue, despite the fact that we have chosen transplant. I hope my presence won't be uncomfortable to those who have chosen to continue dietary management. I do not wish to make a decision for anyone, but I do wish to be available at MSUD Symposiums for anyone who has questions about transplant. While doctors and statistics are important in making a decision, talking to other parents is invaluable - especially parents who are totally honest about the trauma of transplant. I am grateful to those families who have been our mentors on our journey and desire to share what we have learned with others. I believe our presence as Transplant families at MSUD symposiums evidences our support for the group.

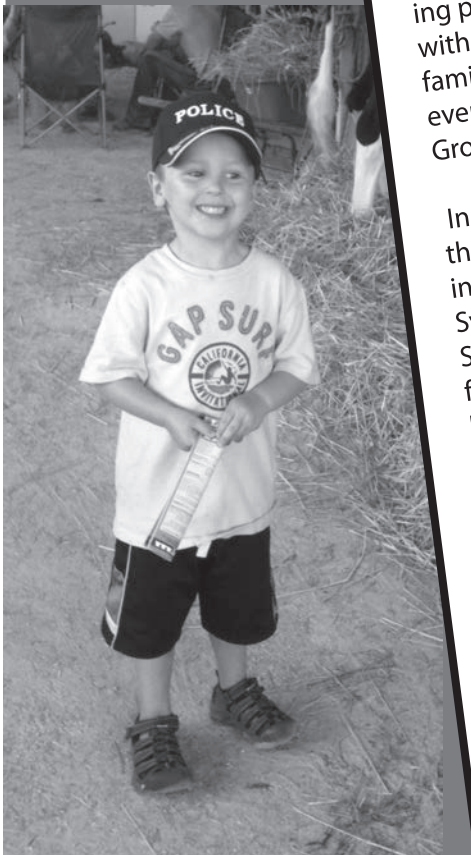


Barbara Mudrick Mom, Dylan age 4, transplanted August 2009

My son Dylan is only 4 years old and I have already attended 3 symposiums even though he was transplanted 3 years ago. At the 1st symposium in 2008 he was only 3 months old and we left him at home with Grandma and Grandpa to attend. We met so many amazing people that I was sad to hear that there were families who were no longer involved with MSUD once their children had been transplanted. While I understand that each family has their reasons, to me the bottom line is that this is such a small community that even though Dylan had the transplant, I will always support the MSUD Family Support Group. And I have. After all, transplantees are still genetically MSUD.

In the spring of 2009 along with 3 other Chicago MSUD families we hosted a fundraiser that raised about \$10,000. Then in August of 2009 Dylan had his transplant. While I was in Pittsburgh, I held calls with Sandy Bulcher and Denise Langosh to plan the 2010 Symposium. I co-hosted the MSUD Symposium with Julie Szymczak, Denise and of course Sandy and enjoyed once again talking with MSUD families from all over the world. In the fall of 2010 I co-hosted another amazing fundraiser with the Dolins family at the Dana Hotel in Chicago, again raising over \$10,000 to support research.

I just attended the 2012 Symposium, and while most of the agenda may not have directly affected my son, I still learned a lot about post-transplant results and research that will affect us forever. I had told our Geneticist, doctors, friends and MSUD families, that my goal is to always be there for the MSUD community, whether it's helping Sandy with hotel stuff or just being there to talk with people whether they have opted for transplant or not. "MSUD is a part of our life" and will always be part of our life. When you think about it, our children are the next generation to support MSUD and can learn so much from both sides of the community. My hope one day is to have more transplant families attend so we can sit down and see how we can support the entire community. My personal wish list is to develop a scholarship program for the young adults and to set up a process for getting formula to people either in the States or abroad that can't get it on their own. There is so much more to do if we want it!





Soft Pretzels

400 grams wheatstarch
1 tablespoon methylcellulose
2 tablespoons psyllium fiber
2 tablespoons brown sugar
2 tablespoons yeast
400 grams water
1 tablespoon oil
1 tablespoon baking powder
4 tablespoons melted butter
Coarse pretzel salt

Combine dry ingredients in a mixing bowl. Add water and oil. Mix well. Let rise for 30 minutes. Mix again. Divide dough into 8 pieces. Roll each piece into a long rope and shape into a pretzel. Add baking soda to 2 cups water and bring to a boil. Dip pretzels in one at a time for 5-7 seconds. Place on a well-greased baking sheet. Sprinkle with coarse pretzel salt. Let rise 5-10 minutes. Bake at 450 degrees for 12-15 minutes or until brown. Dip into melted butter.
8 pretzels

	Protein	Leucine	Calories
Per recipe	3.5g	261mg	2076
Per serving	0.4g	33mg	260

Taco Soup

1 cup tomato sauce
1 3/4 cups water
1/4 cup chopped onions
1 tablespoon butter
1/4 cup uncooked low protein elbows
2 tablespoons corn
1 1/2 teaspoons taco seasoning
3 corn chips
1 tablespoon shredded low protein cheese

Melt butter and sauté onion until tender. Add water and tomato sauce and bring to a boil. Add elbows, corn and taco seasoning and simmer 15 minutes. Ladle soup into bowl and top with crushed corn chips and cheese. 2 servings

	Protein	Leucine	Calories
Per serving	1.35g	116mg	166
Per recipe	2.7g	232mg	332

Idaho Stuffed Squash

2 medium acorn squash
1 cup mashed potatoes
(no added butter or milk)
2 cups low protein bread cubes
1/2 cup chopped onions
1/4 cup diced green peppers
1/4 cup melted butter
1/4 cup liquid coffee creamer
1 teaspoon season salt

	Pro	Leu	Cal
per recipe	8grams	533mg	1167
per serving	2 grams	134mg	292

Preheat oven to 400 degrees. Cut squash in half and remove seeds. Wrap in foil and bake until tender; about 50 minutes. Mix together potatoes, bread, onion, peppers, butter and creamer. Season with salt and pepper. Fill cavity on squash with mixture dividing between the 4 halves. Bake at 350 for 30 minutes. Serves 4. You may freeze the squash after adding the stuffing mixture. Wrap each individually and freeze. Remove from freezer and partially thaw. Bake until the squash is totally heated.

Apple Salad

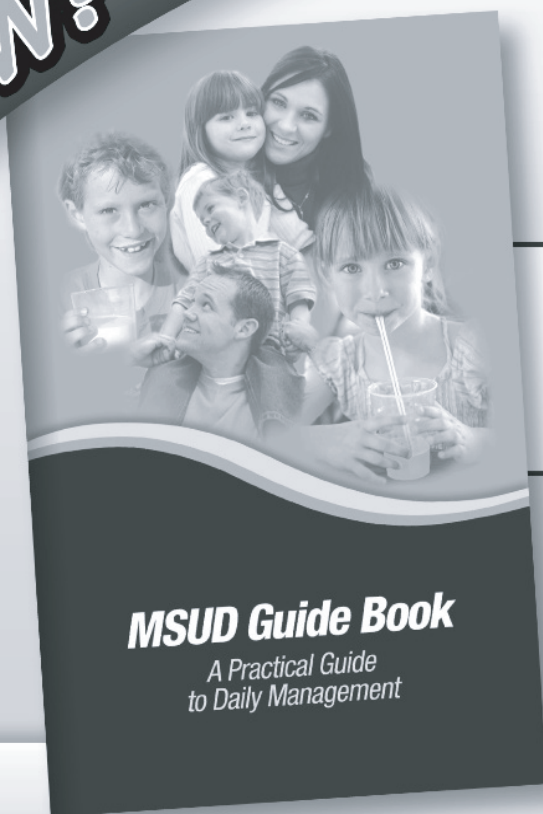
6 cups apples chopped
(mix red and green apples for color)
1/2 cup Golden raisins
2 bananas, sliced
1 cup miniature marshmallows
Dressing;
1 cup sugar
2 tablespoons cornstarch
or clear jel
1/2 cup water

Combine fruit and marshmallows and set aside. Mix sugar, cornstarch and 1/2 cup water together. Bring remaining cup of water to a boil and slowly add cornstarch mixture, stirring until thickened. Add butter and vinegar. Cool. Toss with fruit just before serving. 10-1 cup servings

	Protein	Leucine	Calories
Per recipe	8.4g	390mg	2153
Per serving	0.8g	39mg	215

Please send recipes to
Food News Editor

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Ph: 717-738-4793 • ernieglenda@dejazzd.com

NEW!

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Cambrooke Foods Announces Two New Low Protein Products

Toasted Pierogies & Marinara Minis

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Cambrooke Foods is excited to announce two new low protein food products –Toasted Pierogies and Marinara Minis! Toasted Pierogies are low-protein pasta freshly filled with potato and cheese and covered in a crumb coating. They are perfect as an appetizer or as an entrée!

Toasted Pierogies go great with the other new product, Marinara Minis which are individually packaged cups of marinara sauce. Because Marinara Minis come in a single serving size, they are convenient and easy to take on the road. Marinara Minis are also suitable for low protein pasta products or as the sauce on Cambrooke's Tuscan pizza crusts.

Speaking of convenience, have you tried **Camino PRO[®] Amino Acid Formula** for MSUD? Available in ready to drink pouches, Cambrooke's MSUD formula line comes in fruit punch and piña colada. Each serving provides 15 grams of protein, a blend of vitamins and minerals and fiber.

To try a sample, or to place your order, call toll-free 866-5-456-9776, option 2 or visit our website at **www.cambrookefoods.com**.

Cambrooke Foods can also be reached by fax at 978-443-1318 or by mail at 4 Copeland Drive, Ayer, MA 01432.



"KATIANA WAS HERE"

THE DEVELOPMENT AND EXECUTION OF MY FIRST PROFESSIONAL PLAY

Laura Guthrie

Age 24 / Scotland, UK / Classic MSUD

The Lowdown

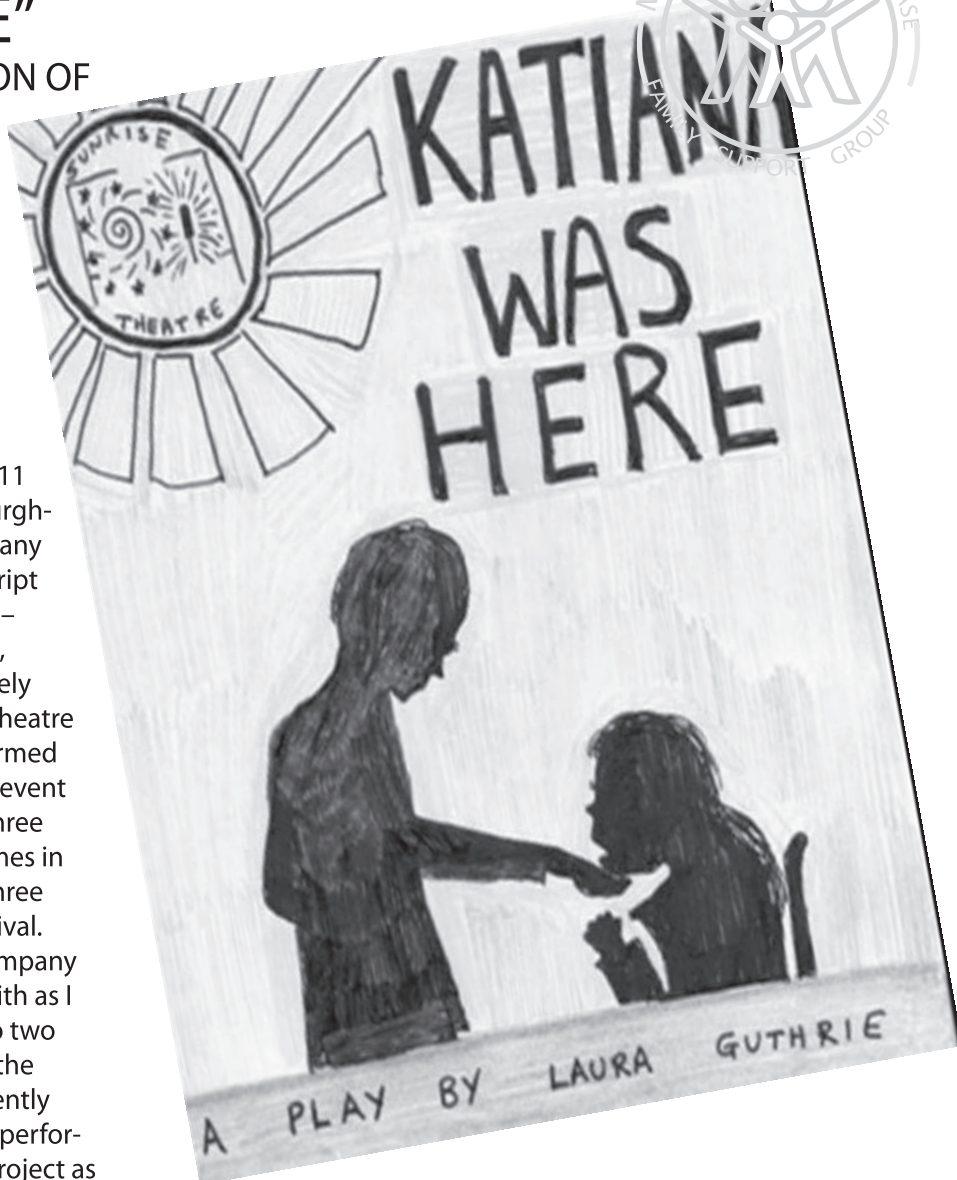
I've always been passionate about the arts. I enjoy painting and drawing, making clay sculptures, composing music, acting and I am currently completing a creative writing course at the University of Glasgow. From February 2011 through this August, with the help of an Edinburgh-based, fully inclusive professional theatre company called edgeeradica, I not only completed the script for my first full length play – "Katiana Was Here" – but was coached through the steps of directing, producing, acting in and scoring it too. Ultimately the experience led to the founding of my own theatre company, "Sunrise Theatre." The play was performed ten times; once in February as a preview for an event hosted by edgeeradica called festival eradica; three times in April for festival eradica itself; three times in June for the Leith Festival and – the big one – three times this August for the Edinburgh Fringe Festival. One of those shows was filmed, and the film company has told me that I can have the footage to do with as I wish. There was a cast of six to eight and one to two technicians. We received three star reviews for the performances in festival eradica, and I have recently discovered a four-star review for the Fringe run performances, which reflects the progression of the project as a whole. I am ecstatic!

The Blurb

Sixteen-year-old Katiana Robinson of Lochendrie, a fictional town in the Scottish Highlands, is a natural-born leader; punchy, spunky, confident, vivacious, a tad manipulative but extremely loving and generous. She suddenly begins having increasing difficulty with movement, speech and vision, leading to the diagnosis of leukodystrophy; an incurable, terminal neurological disorder. The events which unfold as a direct result help to unite her family and friends, taking each of them on their own personal journey of growth, and eliminating past tensions between them. Katiana's painfully shy sister comes out of her shell; her cagey and overprotective mother develops peace and the ability to reach out and accept friendship; and her father, who left the family nine years ago, is forced to reflect upon his mistakes and question his judgements and beliefs, ultimately leading to his re-acceptance into the family.

The Story's Origins

This was a very personal project for me, because it was inspired by two friends whom I lost to an unclassified leukodystrophy when I was thirteen and fifteen. I was only seven when Mum explained to me that because there was no cure for the disease and no way to control it, it would get worse and worse. She did not tell me straight away that my friends would die. I had to actually coax her to say it by asking: "So what happens in the end?" But I knew there was no other possible conclusion. So in a way, the play sprung from the incomprehensible question I had revisited several times over my friends' lives: How does a



(Katiana cont. on page 13)

(*Katiana* from page 12)

person – a person who is perfectly cognitively aware – live a full, rich life knowing they are going to die? The oldest of the girls was the same age as me and equally intelligent and aware. She must have known her abilities were slipping away, and I have no doubt she would have been able to make the logical leap I had made. I realised the only way to explore this, for me, was to write something in first person narrative, from the actual point of view of the person affected – and make them articulate and intelligent enough to be fully aware, and able to express their thoughts throughout. So I created, and entered into, the world of Katiana Robinson.

The Editorial Process

The completion of the script was followed by nearly ten months of read-throughs, casting and re-casting, editing suggestions and stipulations, arrangements and rearrangements.

The Casting

Casting was challenging. Because payment was on a profit-share basis, we didn't attract professional, full-time actors and actresses; those who did sign on pulled out when offered another piece of work with guaranteed pay. So all the people we eventually cast had full-time day-jobs, which in turn affected their availability for rehearsals. I was cast as Katiana's younger sister, Semele, in November 2011, in an attempt to simplify the re-organisation of roles. We looked for potential actors to play the three young roles by attending a college pantomime. We found cast members who were committed, reliable and suited the available parts perfectly.

Problems Along the Way

One of these cast members left us after the festival eradica performances in February, due to his increasing success and demand. Because this young actor had made the role so much his own, it proved impossible to re-cast, and a major re-writing of two scenes in the script followed. After the Leith festival runs, another actor and actress both had to pull out. Whilst we managed to fill the role of the actor with relative ease, unfortunately the first actress we drafted to fill the remaining vacancy was unable to provide the necessary communication and commitment needed, and had to be replaced a week before the Fringe run. Needless to say that pushed my stress levels up! However, one thing I have learned from the play is that for every problem there are always several solutions. Through this experience I've gained a huge amount of confidence in myself and what I can do.

MSUD

Speaking of stress levels, I would like to admit that throughout this process, I don't think I gave my MSUD the respect it demands. I just feel thankful my calorie reserves saw me through on most occasions. I often had to travel from Glasgow to Edinburgh at short notice. The journey

amounted to five and a half hours of travelling round trip, and sometimes I would not get back until after half past eleven at night, or even later. I often forgot to pack food, and since I am the type of person who finds it difficult to raise any health issues with others, I need to take necessary precautions on my own. We often worked over mealtimes and as director I was unable to leave to get food. As time with certain cast members was so rare and precious, I didn't want to waste one second. This meant I often didn't eat until I got back to the flat – or I would have lunch at 5pm following rehearsals, having only had cereal for breakfast and nothing in between. And sometimes I would fill up on just maxijul and formula if I was too tired to cook supper, with a little bit of milk to supply the tiny quantities of natural protein needed. DO NOT TRY THIS. I cut it very thin indeed doing that – and would wake up in the morning nauseous with the shakes. I also forgot to submit Guthrie blood tests each week, as I am supposed to.

My sleeping pattern has always been squiff, but it got especially squiff throughout the production – staying up to 2,3, even 4 pm. I would counter the calorie-burning effects of this with formula and sometimes a late night snack. I consider this "formula abuse" – using formula to aid my MSUD-rule-breaking, rather than to facilitate good health.

I would usually forget to take my formula at lunch. I balked at taking maxijul or vitabite (low protein high calorie supplements). In fact, the only things I did not mess around with at all were the types of foods I am allowed to eat. I did begin trying to pack lunches, and the producer knew about my requirements, but I remained guilty of underplaying the necessity for me to take stricter care of myself, and prioritising the play, literally over everything else. This resulted, on three occasions, in my levels going up to a degree I could physically feel. It happened once during a period of rehearsals, and another time at the end of a cold. The other two episodes didn't happen until the week before the Fringe, and again after the Fringe having attended an unrelated workshop. I managed to control things and stay out of hospital each time by taking extra formula, water and calories, and sleeping. Perhaps it's like how often levels go up when an infection is finishing, because the body's reserves are all used up. I was just burned out.

I am trying to get things together now that I have nothing major on and am not going back to university until September 17th. Reading this now I realise how very lucky I was that things did not get a lot more serious.

The Learning Process

One thing I learned a great deal about from acting, directing and producing the play was that things pile up, regardless of how hard you try to plan ahead, and you have to be prepared for that. Because I now know that this will certainly happen, I will be able to manage my time accordingly in the future,

(*Katiana* cont on page 14)

(*Katiana* from page 13)

making allowances for this and organising my priorities appropriately. I like to think of the production as a wigwam. Each individual member can't hold up the play on his or her own unless they support, and are supported by, every other cast member. If they do support each other though, the production, and indeed the theatre company putting the production on, will be successful.

I had to develop a sense of confidence, authority and ownership when directing. If nobody has ownership of a production, the end result will not feel self-assured, and an audience can't feel easy in watching it. The final thing I have learned from my directing experiences is that there is no one style or way that will suit everyone. Everybody works in different ways, and has their own understanding of what you are asking of them.



Outside of rehearsal time I also had significant input into the administration and marketing of the production. This was a privilege to me both as a writer and a director. It gave me the ability to do all the things I most love and believe I am best at, to have a great deal of control over what was done with my play, and to connect with, and get to know, the cast, crew and processes involved far better than if I had simply written the play and handed it over to a theatre company, or if I had just acted in it, or been directing a play I did not write myself.

Letting Go

Although I had a great deal more influence over the production than the vast majority of writers probably do; and although I will forever be grateful to edgeeradica for providing me with my first opportunity to see my work performed professionally, it still frustrated me that sometimes in the early days I was directing the play under the supervision of the david – the man who runs edgeeradica. He and I can both be equally infuriating to work with at times, and our visions sometimes differed! In order to realise the play under his guidance, I had to let go of



some of my own intentions and ideas. Although this was difficult at first, it was a necessary lesson in working with others. As a writer it taught me what it means to put one's work into the world, where one has much less control over it. Ultimately, I was surprised and delighted that the final performances turned out remarkably similar in feel, look and characterisation, to the version that had been in my head for so long.

Conclusions

I knew as soon as I agreed to work towards a performance that there were only two possibilities: Either the integrity and core messages of the play would be lost, or they would be preserved. I feel very blessed that the people who have worked with me understood and respected the position I was in. It has been both an exciting and terrifying experience in turns. I've gone through periods of extreme anxiety, suspense, self-reflection, and often self-blame. But when those times threatened to get the better of me, I just remembered that every conversation over line interpretations, every tech decision, every cast meeting, was to tell a story that I wrote, about characters from within my heart – and that was, and is, a massive honour.

In amongst everything else, I got my own personal answer to the question that prompted it all. How does a person live a full, rich life in the knowledge that they have a progressive and terminal disease? The real story of the *Katiana* had never been about the disease or what it was doing, even though that had influenced events and interactions. It was about the people, and the love that came out of the whole experience. That was what gave the play its richness and fullness. And perhaps in a similar way, in those circumstances, or indeed any situation where the future is precarious, life is given its richness and fullness. ■

"Just a little note to say what I like about the symposium. I liked the crafts. I liked the DVD called Summer of the Monkeys. Playing Apples to Apples. Looking at the zoo animals and talking about them. I liked to watch the ducks swim. I liked the spaghetti, french fries, and cookies. I liked the Mad Science show. It was fun at the symposium."

-from 9 year old girl with MSUD



Liver Transplantation for MSUD: Current Status and Outcomes

G. Mazariegos, H. Morton, K. Strauss, K. Soltys G. Bond, R. Sindhi

Children's Hospital of Pittsburgh of UPMC,
Clinic for Special Children Strasburg, PA University of Pittsburgh Medical Center and the
Thomas E. Starzl Transplantation Institute

Over the past several years, increasing experience with liver transplantation for MSUD has allowed doctors and families to have a more complete understanding of the benefits and risks of medical therapy and transplant. For the individual with classic MSUD, metabolic decompensation is always a possibility. In addition, the highly restrictive nature of the diet affects quality of life, and the cost of formula and low protein foods can be prohibitive for many. Transplant not only carries risks for potential complications associated with any surgery but there is also the danger of rejection and the need for immunosuppression. The extent to which these latter risks can be minimized is a critical factor in the decision whether or not to transplant.

Liver transplant is a treatment choice for a number of disease states in addition to metabolic disease, with biliary atresia being the most common other indication for liver transplant in children. Data on survival outcome based on diagnosis, though, have shown that survival rates are highest for those with metabolic disease with survival approaching 96% after 5 years in children transplanted at Children's Hospital of Pittsburgh (CHP).

Thus far, 49 MSUD patients, ages 1.4 to 32.1 years, have undergone transplant or are being cared for at CHP. The first was a girl exhibiting vitamin A toxicity. After her transplant, her amino acid levels normalized without dietary restrictions. Subsequently, an additional 48 MSUD patients (classic type) have been transplanted at CHP of UPMC since 2004.

Patient survival for patients with MSUD is 100% currently and no patients have required a re-transplantation. Patients have experienced normal branched chain amino acid levels immediately post transplant, with maintenance of metabolic stability under conditions of unrestricted protein intake as well as inter-current illnesses. In addition to the obvious medical benefits, subjective improvements have been noted in attention span, speech, behavior and motor skills; objective measurements in IQ or cognitive ability have shown no change after transplant.

Historically, the heavy doses of immunosuppressive drugs required long term has had a significant impact on quality of life post-transplant. Cyclosporin, for example, causes excessive hair growth, weight gain, high blood pressure, and bone disease. The ability to taper and, ideally, to withdraw immunosuppressive medications while continuing to prevent rejection is the ultimate goal. Tacrolimus, a newer class of drug, is moving treatment in that direction.

Currently, most of our MSUD patients are on low doses of tacrolimus as their only immune suppressant and only 5 patients are on a low dose of prednisone. None of the CHP patients have incurred any diabetes post-transplant and hypertension has been infrequent. No patient transplanted since 2004 has developed post transplant lymphoproliferative disease (PTLD).

Dr. Mazariegos suggests that individuals with MSUD and their parents consider the following potential indications for transplant:

- Lability of the disease despite optimal medical control and the development of metabolic crisis
- Neuro-developmental sequelae:
 - Attention deficits, hyperactivity in children
 - generalized anxiety and panic attacks, depression, delay in adults
- Dependency on medical enteral formulation
- Intensiveness of medical therapy compared to post transplant therapy

National wide outcome data for all transplant centers is available publically at www.srtr.org or <http://www.srtr.org/csr/current/Centers/TransplantCenters.aspx?organcode=LI>

Dr Mazariegos may be reached at george.mazariegos@chp.edu (email) or phone 412-692-7867 for any additional questions. ■

Cell Transplantation to Treat a Mouse Model of MSUD

Kristen J. (Skvorak) Vallieu, Ph.D.

University of Pittsburgh Medical Center
Depts. of Pathology and Pediatrics

Many MSUD patients have successfully undergone liver transplant to treat the disease. This procedure does not cure MSUD, but the transplanted liver is able to produce enough enzyme to allow a normal diet and to avoid the serious problems that arise with illness. Liver transplant is not without costs, though. It is a highly invasive procedure and carries with it the risk of serious complications including rejection. Lifelong immunosuppression is needed, which carries its own risks. It is expensive, and livers are in short supply. For these reasons, other methods of treatment must be pursued.

Hepatocyte (liver cell) transplantation is one such alternative. It is much less invasive and therefore carries a smaller risk of complications. It is 5-10% of the cost of a liver transplant. Patients keep their own liver, so if failure occurs they are returned to their pre-transplant state, as opposed to liver transplant which would require another liver. Hepatocyte transplantation has been used successfully in the treatment of metabolic diseases in mice. Hepatocytes transplantation has also been used clinically to treat patients with liver failure, and metabolic diseases such as Crigler-Najjar, ornithine transcarbamylase (OTC), glycogen storage disease, citrullinemia, and others.

As described in the earlier newsletter (Fall 2009), we transplanted hepatocytes into a mouse model of intermediate MSUD (1,2). Improvements were seen in enzyme activity (from 6% to 14%), amino acids in the blood and brain, and neurotransmitters in the brain.

Following those studies, we expanded upon our results by testing a potential other cell source, the human placental-derived amnion epithelial cell (hAEC). The amnion is the thin membrane which surrounds the fetus during pregnancy. The epithelium refers to the cells that make up the outer layer of the body. These cells are obtained from the human placenta following full term birth which is a plentiful source of cells, as there are more than 1.2 million c-sections per year in the US. They have been extensively studied in the laboratory of Dr. Stephen Strom at the University of Pittsburgh (3), and have been found to be easy to isolate, maintain in culture, and freeze, and provide a non-controversial source of stem cells. Importantly, they have anti-fibrotic, anti-inflammatory, and anti-microbial characteristics and can evade immune detection.

We transplanted these cells into the intermediate MSUD mouse, and found results similar to liver cell transplant. Growth and survival were greatly improved, there was significant improvement in amino acid levels in both the blood and the brain, activity of the liver BCKDH enzyme (the faulty enzyme in MSUD) was more than doubled, and there was improvement in some neurotransmitters found in the brain. From these results, we have concluded that human AE or other stem cells may provide an alternate source of cells for transplant.

The exciting results of this study have been submitted for publication, and I will provide the reference to the MSUD Support Group once it has been formally accepted. I have also had the opportunity to present these data at The Scandinavian Transplant Society meeting in Reykjavik, Iceland in May 2012 and The Transplant Society meeting in Berlin, Germany in July 2012.

My current work now involves expanding cell transplant therapies to other mouse models of metabolic disease, such as PKU, MCAD, and tyrosinemia. I will also begin investigating induced pluripotent stem (iPS) cells (4) as a potential alternate cell source for cell transplant in addition to hepatocytes and hAEC. Pluripotent means the cells are able to differentiate into any cell type in the body. The exciting prospect of induced pluripotent cells is that researchers have learned how to take adult cells (unipotent, meaning they can only produce cells identical to themselves) and force them to once again become pluripotent just as they were during early fetal development producing a stem cell that is identical to an individual. Therefore, if researchers can collect patient cells to make iPS cells, correct the patient's deficiency in a lab, and then transplant the corrected cells back into the patient to treat their disease, this will eliminate rejection risk and the need for immunosuppression. ■

My previous mentor, Dr. Stephen Strom has relocated to the Karolinska Institutet in Stockholm, Sweden, and I am continuing my postdoctoral fellowship at the University of Pittsburgh with the guidance of Dr. Jerry Vockley, M.D., Ph.D., Dr. Ira Fox, M.D., and Dr. Steven Dobrolowski, Ph.D.

References

- Skvorak, K.J., et al., *Mol Ther.* 2009; 17(7): 1266-73
- Skvorak, K.J., et al., *Biochim Biophys Acta.* 2009; 1792(10):1004-10
- Miki, T. & Strom, S.C. *Stem Cell Rev.* 2006;2(2):133-42
- Takahashi K, et al. *Cell*, 2007; 131(5): 861-872

This article is reprinted from the Summer edition of BC Children's Hospital Foundation "Speaking of Children" magazine

feature story

The Sweet Smell of Trouble

Toddler Grayson McGill has a rare metabolic disorder where regular food can make him ill.

by KERRY GOLD

Chad Farquharson, after a day at his government job, stands by a large schedule posted on his kitchen wall, considering his son's protein consumption for the day. Nearby, his 16-month-old son Grayson sits in his high chair, glued to his favourite show, one involving words. This is not unusual, explains Chad, because Grayson had been read to regularly, since Chad and husband Wayne McGill adopted the baby at birth. What is unusual is that every day, the couple must measure the amino acids consumed by Grayson down to the exact milligrams. If they are off, the results could easily be catastrophic.

Grayson has Maple Syrup Urine Disease (MSUD), a rare and potentially deadly metabolic disorder that causes amino acids from proteins to accumulate in the body. Grayson is unable to process three amino acids — leucine, isoleucine and valine. The disease's saccharine name, which comes from the sweet smell of the patient's urine, belies the seriousness of the condition. The toxicity it causes can lead to brain swelling, mental retardation, coma and death.

Grayson's life will hinge forever on his ability to delicately balance the amount of amino acids he consumes each day. He won't be able to eat cheeseburgers and fries like other kids. As an adult, he'll never sit down to a steak dinner. Meat, seafood and dairy products are like poison to Grayson.

Even his environment can pose a danger. "Playdough has flour in it, and grain has protein," says Chad. "If he swallows the playdough, it can break down in his stomach and release leucine." Not knowing what might contain protein is a worry.





Left: Grayson McGill. Above: Chad Farquharson and Wayne McGill with their son, Grayson. Top right: Dr. Hilary Vallance, head of the BC Newborn Screening Program, with colleague, Dr. Graham Sinclair. Bottom right: Newborn blood is screened for 22 conditions.

Chad and Wayne do not have a medical background, but they have become quick studies in MSUD. Grayson's diagnosis was made just after he'd undergone open-heart surgery to repair life-threatening defects. The operation was successful, but a few hours later, his new parents were told that he had the disease. A neurologist had noticed subtle swelling in his brain and became concerned about a metabolic condition. Because BC Children's Hospital began screening for MSUD as part of an extended screening program that now includes 22 conditions, the neurologist's question was readily answered.

The quick result of the testing meant doctors could instantly respond to Grayson's dietary needs. Dr. Hilary Vallance, director of the BC Newborn Screening Program, developed the framework for the newborn screening test panel review, including the two-year-long selection of disorders to be screened. Colleague Dr. Graham Sinclair, who led the implementation of expanded screening, was the first to spot Grayson's metabolic disorder as it became apparent in the alarmingly big blips on the computer read-out.

"So this baby got appropriate care right from the get-go," says Dr. Vallance. "If we didn't have screening for MSUD, the diagnosis could have been missed entirely and the baby might have died post surgery and nobody would have known why."

As soon as their son was diagnosed, Chad and Wayne learned that proteins are made up of 20 amino acids. For life, Grayson will have to drink a specialty formula that is made up of the 17 safe amino acids. However, because the body needs all 20 amino acids, he will also have to consume the other three, but in precise doses that his body can break down.



Because any physical stress can make Grayson catabolic, a condition where the body must break down its own stores of fat, sugars and proteins for energy, he will also have to avoid contracting the common cold and going without food for a prolonged period. Grayson's care is closely overseen by clinician, Dr. Ramona Salvarinova, and dietician, Alette Giezen. If Grayson should want to play sports one day, Alette would adjust his protein and calorie intake prior to the event. Then there's the fact that nobody will understand his condition, which affects about one in 185,000 babies. Chad and Wayne only know of three other children in the province with MSUD.

Grayson, with his fat cheeks and saucer-shaped eyes, looks like a perfectly normal kid. Nobody will believe that he's forever one chocolate bar away from potential brain damage. "This is what we are concerned about when he goes to school," says Wayne, sighing. "It's not like a peanut allergy, so all he has to do is avoid peanuts. I'll have to be clear: 'All food can harm him.'" 🌞



MSUD A sense of Progress 1986-2012 Beyond Survival "What Do We Mean by Successful Treatment?"

**Dr. Holmes Morton, Director
The Clinic for Special Children**

Dr. Morton and his wife Caroline established The Clinic for Special Children in Lancaster County, Pennsylvania in 1989. The clinic provides care for children and adults with inherited disorders common to the Old Order Amish and Old Order Mennonite populations. The Clinic currently follows approximately 115 individuals with MSUD.

Dr. Morton notes that tolerance of dietary leucine declines as a child ages and the rate of growth slows down. Mennonite infants, who all have the classical form of MSUD, tolerate an average of 60 milligrams (mg) leucine per kilogram (kg) body weight per day. This decreases to 20 mg per kg per day as growth slows between 12-24 months of age, and decreases further to 10-15 mg per kg per day in adults. Tolerance of Leucine, Isoleucine & Valine reflect the rate of growth and protein acquisition - human protein is about 10% by weight leucine and 6% by weight isoleucine & valine. During illnesses tolerance of leucine becomes zero or negative as protein within liver and muscle are broken down as a result of the body's response to the stress of infection and an inadequate calorie intake.

In the early years, the prognosis for children born with MSUD was grim. From 1963-1989 the death rate was 55% due to cerebral edema, and cognitive impairment typically occurred. Now, with the benefit of early diagnosis, children experience far fewer hospitalizations and less cognitive and physical impairments. Testing has shown the average IQ in Clinic patients with MSUD to be 95, well within the normal range. We now know that high levels of leucine will result in a deficiency of other amino acids in the brain and contribute to poor growth and function of the brain. Low levels of the amino acid tyrosine, for example, will lead to a deficiency in the brain neurotransmitter dopamine. Recent studies have shown Dr. Morton that the chronically low ratios of valine to leucine (normal value 2) predict poor intellectual outcome. The liver normally keeps the concentration of valine twice as high as leucine and this 2/1 ratio helps assure delivery of valine to the brain and other tissues. High valine levels are not toxic; low valine levels cause trouble.

The most common cause of hospitalization for those with MSUD is infection, common surgical problems like appendicitis, and injuries like broken limbs or car accidents. It is particularly important for those with MSUD to be vaccinated for protection against preventable infections. It is essential that families know where to go for appropriate

treatment, and that care be provided by hospital staff and physicians that are appropriately equipped and experienced treating metabolic illness of MSUD. Families should have a copy of MSUD Gene Reviews or other publications describing management of illness and cerebral edema and an individual treatment protocol. All ill patients with MSUD have some degree of cerebral edema. Dilute IV fluids and hyponatremia in the setting of high leucine levels will make cerebral edema worse. Gene Reviews and other publication from the Clinic describe the management of cerebral edema using mannitol, Lasix, and hypertonic saline. When patients are ill, vomiting, and metabolic control cannot be maintained by oral MSUD formula then BCAA-free total parenteral nutrition (TPN) is needed to prevent further protein catabolism and progressive cerebral edema. Once plasma leucine values increase above 1000 uM (13 mg/dl) in a patient that is ill and vomiting, recovery without IV therapy is unlikely. Vomiting because of rotavirus or because of appendicitis also requires MSUD-TPN. Regional hospitals where MSUD is treated should have this solution available within 4-6 hours after admission. Our Community Hospital, Lancaster General Hospital, uses premixed dry amino acids and can provide BCAA-free TPN within 4 hours after admission. Pre-mixed amino acid solutions can be obtained through Coram Specialty Infusion Services www.coramhc.com/ and stored in regional treatment centers.

Dr. Morton, families, and patients report that liver transplant improves quality of life. Upon transplantation, the disease is immediately controlled, normal dietary protein can be tolerated, patients are protected against catabolic intoxication during illnesses, and cerebral edema is prevented. Liver transplantation will not correct existing cognitive impairments and neurological disabilities. Attention deficit disorder, anxiety, and mood disorders remain problematic. Our recent studies show that after transplant the concentrations of the branched chain amino acids remain slightly high and other important amino acids like tyrosine and tryptophan are relatively low and are therefore still not transported into the brain at normal rates. We are hopeful that some psychological problems like ADD and anxiety may respond to selective supplements of amino acids to correct these more subtle biochemical imbalances.

A stem cell transplant was done on a child with MSUD and

(Dr. Morton cont on page 20)



VitaFlo offers a comprehensive range of specialized products for the dietary management of Maple Syrup Urine Disease (MSUD)

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Innovation in Nutrition

(*Dr.Morton* cont from page 19)

severe immune deficiency. He has become gradually more tolerant to leucine, now tolerating 25-30 mg/kg-day, and he maintains more normal ratios of valine/leucine, which suggest some stem cells may have populated his liver and provided some enzyme activity. Regardless, these changes have developed slowly, over several years, and we recently saw a significant increase in plasma leucine associated with the stress of a broken leg.

Dr. Morton hopes to be able to translate their Clinic for Special Children model, which integrates general medical care and care of MSUD in the out-patient and inpatient setting, to centers where care is now fragmented and available at limited times. ■

PAPERS ABOUT MSUD FROM THE Clinic for Special Children

- 1) Maple Syrup Urine Disease - GeneReviews™ - NCBI Bookshelf www.ncbi.nlm.nih.gov › NCBI › Literature
- 2) Classical maple syrup urine disease and brain development: principles of management and formula design. Strauss KA, Wardley B, Robinson D, Hendrickson C, Ridera NL, Puffenberger EG, Shelmer D, Moser AB, Morton DH. *Molecular Genetics and Metabolism* 99 (2010) 333-345.
- 3) Strauss KA and Morton DH. Branched Chain ketoacid dehydrogenase deficiency: Maple syrup disease. (2003) *Current Treatment Options in Neurology*. 5:329-341.
- 4) Morton DH, Robinson D, Strauss K, Kelley RI: (2002) Diagnosis and Treatment of Maple Syrup Disease: A Study of 36 Patients. *Pediatrics*. 109, 999-1008.
- 5) Mazariegos GV, Morton DH, Sindhi R, Soltys K, Nayyar N, Bond G, Shellmer D, Shneider, Vockley J, Cropcho L, Strauss KA. Liver transplantation for classical maple syrup urine disease: long term follow-up in 37 patients and comparative UNOS experience. (*Journal of Pediatrics* August 2011 www.jpeds.com.)
- 6) Strauss KA, Mazariegos GV, Sindhi R, Squires R, Finegold DN, Vockley J, Robinson DL, Hendrickson C, Virji M, Cropcho L, Puffenberger EG, McGhee W, Seward LM, Morton DH. Elective liver transplantation for the treatment of classical maple syrup urine disease. *Am J Transplant*. 2006 Mar;6(3):557-64.



Clinical Hepatocyte Transplantation for Metabolic Liver Disease

Dr. Ira Fox

Rather than undergoing the major surgery involved in liver transplantation, what if liver cells could be introduced relatively easily into a patient's own liver? Would the improvement in enzyme function be enough to improve quality of life for patients with metabolic diseases?

Dr. Ira Fox has been exploring this line of research for years. In hepatocyte (liver cell) transplantation, the liver stays in place and only a small incision is needed. Liver cells are infused through a tube in the umbilicus (belly button) into the blood, where they are then taken up by liver. Animal studies have proven this method to be effective at temporarily treating metabolic disorders, and the technique has been used in humans to treat the metabolic liver disorder Crigler-Najjar Syndrome, an abnormality of bilirubin metabolism which can lead to brain damage. While not a cure, temporary improvements have been observed in enzyme activity. A PKU patient has also received hepatocyte transplantation. Phenylalanine levels were improved for a time, but returned to previous levels after 3 months. While only 9% of the defective enzyme in MSUD is found in the liver, hepatocyte transplantation holds promise as a minimally invasive method of improving activity. As with liver transplantation, drugs must be used to suppress immune function to prevent rejection, which carries short and long term risks.

While many challenges must be overcome, Dr. Fox plans to continue to explore the feasibility of safely and effectively using this technique in MSUD patients. ■

HAVE AN ANNOUNCEMENT YOU WOULD LIKE TO MAKE?

Contact the Editor:

Karen R. Dolins– krdhed@aol.com

19th Annual Metabolic Camp Emory University (Atlanta, GA)

***Join us June 24-29, 2013 for the 19th
Annual Metabolic Camp at
Emory University in Atlanta, GA!***

This is a model, research-based camp for young women 12 years age and older with PKU and MSUD, which focuses on building social support through a variety of activities including nutrition education, cooking classes, discussion groups, and local field trips. The camp typically accepts 30 attendees on a first-come, first-served basis. Registered dietitians from across the nation and around the world volunteer their time to serve as camp counselors, and nutrition students provide support as assistant counselors.

The cost of the camp is \$325 per person, which includes all sponsored meals, lodging, group activities, and field trips.

Partial scholarships are available for certain financial circumstances.

Check with your local RD and clinic to see if local sponsorship is available.

More information about the Metabolic Camp will be available at
www.metcamp.org.

Contact Rosalynn Blair
(Camp Coordinator) at
(404) 778-8521 or rborlaz@emory.edu.



Congratulations!
Brittany Fuller & Shawn Richards were married
in Columbus, Indiana on September 1, 2012
Wishing you a long, happy and healthy life
together!

Annual Fundraising Auction to benefit the Clinic for Special Children

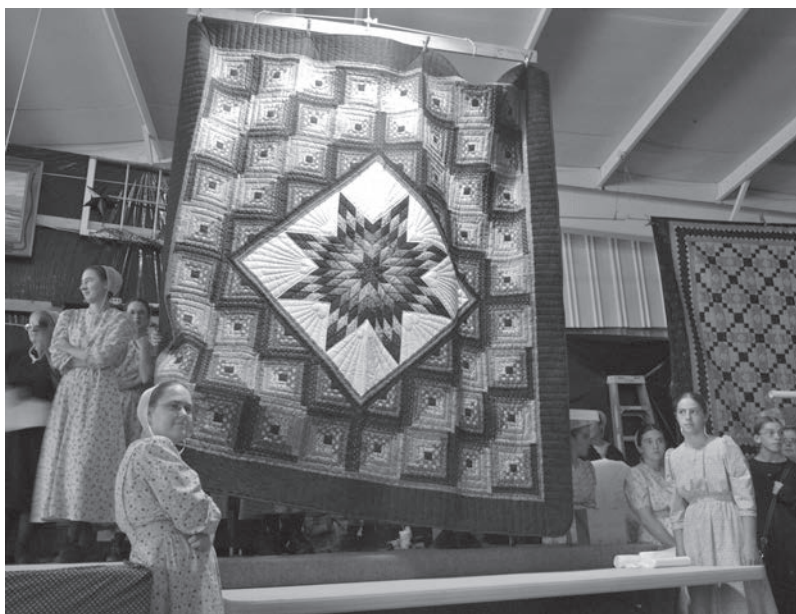


The Clinic for Special Children
held its annual auction on
Saturday September 15th in
Leola, Pennsylvania.

It was a beautiful, sunny day and
the "house" was packed.
The car lot and the horse and buggy
lot were equally full.

Quilts, furniture, plants, baked
goods and more were all available
to the highest bidder.

It was great to see our MSUD
friends, several of whom were
helping out. Hannah Dolins came
home with a stunning quilt.



Karen R. Dolins, EdD, RD, CSSD, CDN

SYMPOSIUM 2012



280
Attendees



10 with Liver Transplants



June 28, 29, 30
Philadelphia, PA

From all over the US
and the World



69 Individuals with MSUD

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