SEARCHING FOR A CURE HOPE FOR OUR CHILDREN

Propionic Acidemia Foundation

VOLUME 1, ISSUE 1

AUGUST 2006

FOUNDATION NEWS

Welcome to the first edition of the PAF newsletter. The objective of the newsletter will be to inform new and existing families on our fundraising progress, provide updates on new treatments and research, and communicate with our PA families and contributors. This last year has marked a successful and productive year for the PAF. We have a new website that will make it easier for families to navigate for the information that matters most. There is a family list–serve where families can log on and post questions and a translator to reach families that speak other languages. We have a state by state resource that enables families to see what resources are available to them in their state. We also had a wonderful year in fundraising. Our PA community raised a total of $40,000. The PAF was able to grant the $40,000 to two researchers. Thank you to all of the families and friends who made that possible through fundraising and donations.

PROPIONIC ACIDEMIA FOUNDATION

PA FAMILY DAY OCTOBER 7TH 2006

This October we have our first PA Family Day. Jill Franks, the President of the PAF, is hosting this fun filled event in her home in Highland Park, IL. There will be lots of fun things for the kids to do and plenty of low protein foods. What a great opportunity to be around a community of people who experience the daily life of PA. All PA families and friends are welcome. Please RSVP if you would like to attend.

When: Saturday Oct. 7th

Where: Highland Park, IL. (just outside of Chicago)

For more details and to RSVP contact Jill at:

1-877-720-2192 toll free

www.pafoundation.com

PA Families Needed

The PAF is looking for PA family volunteers. There are several projects that the PAF is working on that could use your help.

If you are interested in volunteering some time to the PAF please feel free to contact us through email or our toll free line.

We look forward to hearing from you!

paf@pafoundation.com

1-877-720-2192 toll free

INSIDE

THERAPEUTIC APPROACHES TO PROPIONIC ACIDEMIA

"THE HOPE IS THAT THIS APPROACH CAN BE INTRODUCED IN CLINICAL PRACTICE AND HELP SOME PATIENTS TO OVERCOME THEIR METABOLIC DISEASE"

The strength of our research lies in the finding that some forms of mutant PCC are very responsive to an addition of small chemicals called chemical chaperones. These altered forms of the enzyme are not deficient in their ability to carry out the enzymatic reaction but rather in their ability to form the proper structure and assume the correct shape. The chaperone helps them to fold with a large increase in activity. We have carried out the initial experiments on normal and three mutant forms of PCC in a bacterial system in which the human enzyme can be manufactured. Later, we have used the chaperones in skin cell cultures derived from controls and propionic acidemia patients. Again, in some cases we saw large increases in PCC activity. We will continue to screen different chemicals and different mutations for their ability to yield more active PCC.

The hope is that this approach can be introduced in clinical practice and help some patients to overcome their metabolic disease. The real promise is that some of the drugs, which gave us the best results, are already in use in clinical practice to treat other disorders.

By Jan P. Kraus Ph.D. Professor, Department of Pediatrics UCDHSC at Fitzsimons

On going research by Dr. Kraus can be viewed at: www.uchsc.edu/cbs/pcc/about_pcc.htm

FUNDRAISING AND HOW YOU CAN HELP

The PAF is excited for what we have accomplished in the past year. This year the PAF is committed again to using over 90% of funds donated to provide research grants and offer support activities, but we can not do this without you! Studies have shown that in order for a non-profit group to continue to operate each year they need over 75% of their donations to come from individuals. The following is a list of simple things you can do to work towards better treatment and a cure for those with propionic acidemia. Find a couple of items that you can commit to doing in the next 12 months, so there can continue to be "Hope for our Children".

EASY IDEAS FOR FUNDRAISING

- There is a new and easy way to raise money for the PAF just by searching the Internet with GoodSearch.com. It's simple. You use GoodSearch.com like any other search engine — the site is powered by Yahoo! — but each time you do, money is generated for PAF. Last year, search engines generated close to $6 billion in revenue from advertisers. With GoodSearch part of this advertising revenue will now be directed to PAF. Just add Propionic Acidemia Foundation in the "I'm Supporting" box and every time you surf the net PAF will get money! We hope that not only will you use GoodSearch as your main search engine from here on out, but will also pass this message on to your friends and family. The more people who use this, the more money will go to PAF.
- Like to help Your Cause? Indulge in chocolate, satisfy your craving for that new CD, and spoil yourself with the latest software. In short, buy all those things you want and need. And don't worry. When you shop at the Mall at iGive.com, your purchases come guilt-free because up to 26% of each item you buy will be donated to the PAF at no extra cost to you.
- Ask your employer if they offer matching funds for donations to non-profit organizations. Many will give an additional 50-200% of your donation amount, so talk to human resources or your manager before making a donation.
- Host a garage sale and donate the proceeds to PAF. Have informational brochures about PA and PAF with a donation slip attached available, so those attending have the opportunity to make a donation as well.
- Ask for donations to PAF in lieu of gifts for holidays and birthdays or for funerals of a loved one.
- If you live in near a Food Co or in Southern California, Nevada, Indiana or Illinois near a Food 4 Less contact PAF for information on their Community Rewards Program. If you use the Community Rewards swipe card at their stores they will donate 4-5% of your purchase total to PAF.
- Shop for yourself or a friend at www.cafepress.com/pafamily. A portion of the sales price will be donated to PAF.

LOOKING FOR OTHER FUNDRAISING IDEAS? CONTACT THE PAF FOR OUR NEW FUNDRAISING PACKET. EVERYTHING YOU NEED TO SUCCEED!

cafépress.com

GoodSearch

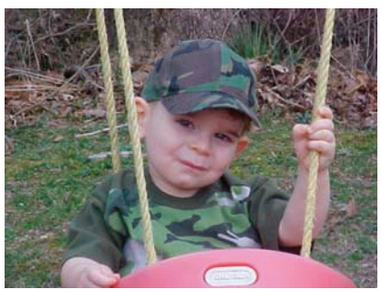
iGive.com®
Change online shopping for good.

PA Family Spotlight– Trenton David McKinley

Born on April 21st of 2002, Trenton David McKinley was born special. We knew that he was going to be special (and a little spoiled), he was the first grandchild on both sides of our families.

Little did we know just how special he was going to be. After having a typical uneventful pregnancy, he was born a bigger boy than we expected. 8 lbs 7 ½ oz's & 21 inches long. We took him home & started our new life together. For a few weeks, we thought we had the best baby ever. He slept soundly with us having to wake him up to eat & he never really got upset. Then the signs started… at about 3 weeks of age. He developed thrush in his mouth, had hiccups a lot & was constipated. The pediatrician assured us that all of this was normal. But on May 27th, we saw with our own eyes that something was not normal. Trent was lying on a blanket in the middle of our living room and starting having a seizure. It lasted only a few minutes then he was fine. Then a second seizure followed.

After arriving at Kosair Children's hospital in Louisville, KY – he was immediately put on Phenobarbital, and had an EEG, MRI, & CT scan. He had seven seizures total that day. That next day, we met an angel right here on earth. Our neurologist, Dr. Vinay Puri. Without this man, our little Trent would have not be alive today. After a couple days of constant blood work, numerous tests and a muscle biopsy, Dr. Puri told us that he believed Trent had Leigh's Disease. The life expectancy of Leigh's disease is 5 to 6 years. Of course, our families were devastated. We were in the hospital for eight days on our first stay, so were ready to go home and enjoy what time that we had left with Trent. We went home from the hospital with instructions to take 7 or 8 over the counter vitamins/ medicines. On our first night at home, Dr. Puri called and proclaimed the good news that Trent didn't have Leigh's but he had PA.



Knowing only that PA had to do with protein, we thought "Oh wow, we will have to buy everyone a cookbook so that we make Trent friendly dishes." Little did we know, that PA would impact so much more than our cooking. The first month of officially knowing it was PA was rough, going for blood work every few days to check Trent's levels. Dr. Puri, who had never heard of PA before now, was communicating with Dr. George Hoganson for guidance on how to treat it. We were put on Carnitine, Biotin & Propimex 1. We could see Trent staying awake for longer amounts of time so we knew that we were on the right track. The feedings were still a battle though after a 4 oz bottle feeding, we would hold him in our arms for an hour or more to avoid the refluxing or projectile vomiting. This went on for a few months and then in July we ended up back in the hospital because we couldn't get him to eat. He was becoming life less again. By this time, we had been introduced to OAA. While at our July hospital stay, we urged for a g-tube & Nissan. Dr. Puri agreed that it was the right thing to do. We were in the hospital for 18 days (and we thought 8 was a lot before!). Going home with the G-tube, we were finally able to meet the real Trent. It was like a miracle. Being able to get all of his needed calories into his system, he immediately become alive. We have a photo album and it makes you so sad just to look at the photos taken of him before the g-tube was placed. The g-tube was definitely the best choice for us. There had been so many days in his first few month of life, where he didn't even have the energy to cry even during a blood draw. So these days, his just hearing him cry was music to our ears.

With PA in our life, daycare was out of the question so my husband decided to work on a second shift schedule with his hours being from 3 – 11 pm. After a few more months, I finally went back to work and my hours are from 9 – 5 pm. Since our work hours overlap, Trent's grandmother picks Trent up each day. She will stop & pick up Trent around 2:30 in

TRENTON DAVID MCKINLEY

the afternoon and takes him to her house until I am off work. Our lives were getting some routine to them, not a typical family routine – but it's ours. We had adjusted our schedules and outings to accommodate his every 3 hour tube feedings. Trent did really well for about a 4 month stretch, only requiring one quick 2 day stay in the hospital for fluids until Nov 2002. In Nov, he and I came down with a nasty stomach virus. This resulted in another 18 day hospital stay for us. Thanksgiving was nearing and we desperately wanted to be at home for the holidays. But Trent could not get rid of the diarrhea. While feeling desperate for some helpful medical advice, we got in touch with Julie Hardin in Lexington, Kentucky. She put us in touch with Dr. Rani Singh at Emory Genetics. Thru the advice of Julie & Dr. Singh, his diarrhea was finally stopped and we were released from the hospital the day before Thanksgiving. Since then, Dr. Singh follows Trent. She is another angel right here on Earth. She has helped us weather that same stomach virus since at home without a hospital stay.

As the 2003 year went by, things were getting progressively better for Trent. His early intervention was in full swing with PT, OT, Nutrition Services, & Speech. Our therapists proved to be awesome. At around 10 months old he sat up alone. begin crawling at around 14 months & walking at 19 months. The speech & eating parts were (and still are) by far the hardest. Trent said his first word, "MA MA" at around 23 month of age. Knocking on wood, the Nov 2002 has been our last hospital stay. Trent is 4 years old now & still delayed in every aspect but he is making progress daily. I would compare him to a 2 ½ year old child. He is doing much better with OT & PT. His attention span is still very short and he typically wants to play things "his own way". His speech has really picked up lately too, although some of it is still hard to understand. His vocabulary probably consists of about 50 - 75 words and lately he is really into repeating what he hears. He will sometimes put a 2 to 3 word sentence together. He has private feeding therapy every other week. At this time, he gets nothing by mouth and will only drink when forced. Currently his feedings are every 3 hours with three oz of juice given between each formula feeding. At night, he is hooked up to an overnight pump. Having a tube feeding every hour & a half can be a little time consuming but since Trent has done so well with it, we prefer to just let it be. Outings are normally planned around the feeding schedules & the weather. We aren't giving up hope that one day when eating becomes a social issue then he will want to take part and eat by mouth. He did attend preschool two days a week last year. He had terrible attendance (he was only there for 15 days) because he was always carrying home the latest germ. His 2nd year of preschool will be starting very soon. It is so hard to "let go" & send him to school – but we know that he needs the socialization side of school. His grandmother works at the same school, so it is comforting knowing that she is always nearby.

Trent loves typical kid things – singing, coloring, playing in rocks, feeding the fish at his Papa's & Nana's house, & riding the four wheeler with his Pap. He is such a joy to be around. He has such a happy spirit about him (that is until you pull into his doctor's office). We hope & pray that the next few years find us having a healthy Trent who is continuing to talk up a storm & eat some by mouth. We know that God sent us a special child for a reason & even though PA causes our family stress on a daily basis, we know that God blessed us when he chose us to be the ones to take care of such a sweet little boy.

We would like to take this opportunity to say "Thank You" to Judy Ashbaugh, Trent's grandmother, who helps out our family greatly on a daily basis. She is such a blessing to us and we don't know what we would do without her in our lives.

Sincerely, The McKinley's

GENE THERAPY FOR PROPIONYL COA CARBOXYLASE

The Barry Laboratory at the Mayo Clinic is working on a project to test if gene therapy can be used to treat Propionic Acidemia. To test this, PA mice from Dr. Miyazaki are being used as subjects for delivery of the PCCA gene to their livers. Sean Hofherr, a graduate student in Dr. Barry's laboratory is pursuing this project for his Ph.D. thesis. To date, Sean has generated a series of gene therapy vectors expressing either the human or the mouse PCCA gene for testing in the PA mice. Preliminary experiments in the mice indicate that the vectors can be used to deliver PCCA gene to the liver to express amplified amounts of the protein. Work is underway to determine how this modifies the blood levels of propionate metabolites and to what degree this rescues the whole body and neurological symptoms of the disease in the mice. In the process of this work, Dr. Barry's group generated antibodies against different parts of the PCCA protein to help in tracking where, when, and how much of the PCCA protein was being produced by their gene therapy vectors. With these tools in hand, as a side project, their group has also used them to probe some of the basic biology of the PCCA protein. While much is known about the genetics and disease symptoms of PA, little data can be found in the literature regarding the distribution of PCCA protein in different tissues. For example, the level of protein expression in different tissues may explain (in part) some of the tissue damage and symptoms due to loss of PCCA. Likewise, knowing where PCCA is and is not expressed might better guide how transplantation and gene therapies need to be applied and how this might differ between a mouse model and humans. For example, one might predict that the liver expresses the highest level of PCCA given its role in metabolizing excess amino acids and fatty acids. Conversely, one might predict that the brain or the basal ganglion might express lower amounts of PCCA, since many of the symptoms of the disease are manifested in these sites, particularly if these are due to effects within individual cells rather than due to metabolite overload.

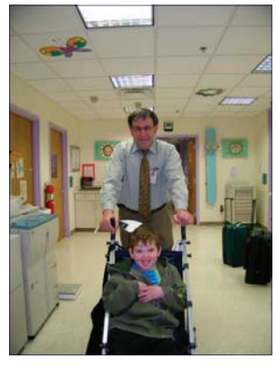
Given these issues, Dr. Barry's group used these new antibodies to screen for PCCA protein production in mouse and human tissue panels. While they expected PCCA to be either ubiquitously expressed or expressed at highest levels in the liver, to their surprise, they observed a marked variation in amount of PCCA in different tissues. In both mouse and human tissues, the kidney appeared to have the highest levels of PCCA protein, in fact higher than in the liver per unit protein. In contrast, in the brain, PCCA was undetected in mouse (but not necessarily zero), and was detectable, but at low levels in the human brain samples.

This data suggests PCCA is not ubiquitously expressed at high levels in all tissues and that the kidney may play a significant role in elimination of Propionic metabolites. While the kidney had higher levels of PCCA when equalized for protein in the different tissues, it should be noted that the liver is still substantially larger in size and so likely "handles" substantially more metabolites. However, better knowledge of the locations of PCCA and cross-talk between organs may assist in optimizing therapeutics and to avoid mis-steps when translating between mouse models and PA patients. Work is underway to screen more specific regions of the brain for PCCA expression and to track how the protein's expression may change over time in the PCCA mutant mice.

Michael Barry, Ph.D, Mayo Clinic

CARBAGLU STUDY IN PA PATIENTS

N-acetylglutamate (NAG) is a chemical produced in the liver that is essential for normal function of the urea cycle; without it, the cycle does not do its job of detoxifying ammonia. Patients who are deficient in NAG in the liver develop hyperammonemia. There are several causes for NAG deficiency. The most obvious is a genetic defect in N-acetylglutamate synthase (NAGS), the enzyme that produces NAG. Other causes involve secondary NAG deficiency due to interference with its production by NAGS. The most known cause for secondary NAG deficiency is propionic acidemia (PA) where the accumulation of propionyl-CoA in liver mitochondria interferes with NAG production. Methylmalonic acidemia (MMA) presumably manifests the same problem. Similarly, patients treated with valproic acid may also develop low liver NAG due to interference with NAG production by valproic acid metabolites. All latter conditions are associated with hyperammonemia presumably due to NAG deficiency. Since we have recently shown that the drug Carbaglu® (N-carbamylglutamate) restores to normal urea cycle functions and eliminates the hyperammonemia in patients with NAGS deficiency, we further hypothesize that patients with PA and MMA who have hyperammonemia may also benefit from this drug. In order to investigate this hypothesis, we have launched a study in patients with severe PA and MMA (those who presented with neonatal hyperammonemia). The study is open to patients with severe PA or MMA who are 5 years and older and consists of oral administration of a stable isotope [13C]sodium acetate before, and following 3 days of Carbaglu treatment, comparing the mount of [13C] that ends up in urea as an indication of urea production rate. One patient with PA who was studied showed a marked increase of urea production on Carbaglu as well as decrease in glutamine and glycine levels. If this finding can be reproduced in additional patients with PA or MMA, it will suggest that Carbaglu could effectively treat hyperammonemia episodes in patients with the most common organic acidemias. Although hyperammonemia is only one of the several mechanisms of metabolic derangement in PA or MMA, alleviation of hyperammonemia could facilitate the management of these patients.



Jordan Franks (PA) and Dr. Tuchman during Jordan's Carbaglu Study

By Mendel Tuchman M.D.
Vice Chairman for Research
Scientific Director, Children's Research Institute
Professor of Pediatrics, Biochemistry & Molecular Biology
Children's National

If you are interested in learning more about this study and enrolling your child or self please contact;

Dr. Mendal Tuchman
Children's National Medical Center
111 Michigan Ave. NW
Washington, D.C. 20010-2970
Office: (202) 884-2549
Fax: (202) 884-6014
Lab: (202) 884-3991
mtuchman@cnmc.org

Thank you to our Corporate Sponsors:

Vitaflo USA

Zevex

SEARCHING FOR A CURE
HOPE FOR OUR CHILDREN

Propionic Acidemia Foundation
1963 McCraren Rd.
Highland Park, IL.
60035

Phone: 1-877-720-2192 toll free
Fax: 1-877-720-2192
E-mail: paf@pafoundation.com

WE'RE ON THE WEB!
WWW.PAFOUNDATION.COM

Thank you to :

Publishers Printing Company

for their contribution of printing the PAF Newsletters

PROPIONIC ACIDEMIA FOUNDATION

We would like to acknowledge and thank a few people who have made an impact on the PAF this last year. Thank you to three board members who have moved on to pursue other endeavors. Ruth Milne, Janice Boecker, and Kathy Stagni. We wish them all the best and thank them for their time and contribution to the PAF. Thank you to Mary Cartwrite for creating such a beautiful and user friendly web site. Mary donated her time and expertise to our website and we are truly grateful.

To our PA families who believe in the PAF and that together as a community we can achieve our vision of creating a future where Propionic Acidemia can be prevented and affected individuals can be cured to lead a productive and healthy life.