

Propionic Acidemia Foundation

VOLUME 1, ISSUE 15

FALL 2013

2013 PAF Conference- A Volunteer's Perspective

By Ryan Franks

On June 28th and 29th, I volunteered to help with the 2013 PAF Education Conference in Denver, Colorado. On Friday, having been appointed as the Official Photographer, I visited Dr. Kraus's laboratory. During this trip, Dr. Kraus took us on a tour of his workplace and explained the function of the lab equipment as we passed by it. It also had a Dr. Who themed whiteboard! It was very cool, especially the walk-in refrigerator. At the end of the tour, we



Ryan and Dr. Kraus in the lab

got to ask Dr. Kraus questions and he explained a bit about his research. Following this, I assisted in assembling goody-bags including the donations of Green Mountain Coffee and Cambrooke Foods. These would be distributed to the families at the conference. The next morning, I awoke early and helped prepare the registration table for the conference.

During the conference, we had four speakers. First, Dr. Chatfield spoke about "Cardiac Issues in Propionic Acidemia (PA)." Specifically, she gave us details regarding cardiomyopathy and Long QT. We learned about the relationship between those issues and PA as well as how they are diagnosed. Furthermore, we learned about treatment options and their benefits and risks.

Afterward, Dr. Gallagher gave her presentation on "N-Carbamylglutamate in the Treatment of Hyperammonemia in PA and MMA". Also referred to as Carbaglu, N-Carbamylglutamate is meant to help process ammonia and could potentially be very helpful to people with Propionic Acidemia. Dr. Gallagher is currently working on a study to determine whether Carbaglu is effective in PA patients.

Later after lunch, Cindy Freehauf lead a fun and informative activity titled "Let's Play with DNA." She taught us about the different types of mutations like deletions and the potential effects they could have. We then participated in a mini-lab experiment and extracted DNA from seeds using various household items. (Continued on pg. 3)

Connor William
McKillop



July 2, 1992 -
June 25, 2013

(page 6)

INSIDE

A NEW MODEL FOR THE STUDY OF PA	2
ANAPLEROTIC THERAPY IN PA	3
PAF CONFERENCE (CONTINUED)	3
LUCY'S STORY	4
LUKA'S STORY	5
FUNDRAISING SPOTLIGHT	6
CONNOR'S TRIBUTE	6
PAF ANNUAL REPORT	7

MISSION: The Propionic Acidemia Foundation is dedicated to finding improved treatments and a cure for Propionic Acidemia by funding research and providing information and support to families and medical professionals.

VISION: To create a future where Propionic Acidemia can be prevented and any affected individual can be cured and live a productive life.

A NEW MODEL FOR THE STUDY OF PROPIONIC ACIDEMIA

by Adam J Guenzel and Michael A Barry

Gene therapy research for propionic acidemia in the Barry Lab at Mayo Clinic has been supported by the Propionic Acidemia Foundation. Our work has focused on development of adenoviral and adeno-associated virus (AAV) vectors to deliver either the PCCA or PCCB genes to correct deficiencies in propionyl CoA carboxylase (PCC). We began testing gene therapy in the original PA mouse model generated by Dr. Miyazaki in which both copies of the *PCCA* gene were inactivated. While testing could be performed, total loss of PCC activity in the mice resulted in a 36-hour lifespan and made analysis of disease and testing therapies difficult.

To provide a more tractable model, we introduced a human gene encoding PCCA with an A138T mutation that was identified in a patient with propionic acidemia in Dr. Ugarte's lab at Universidad Autónoma de Madrid. In collaboration with Dr. Jan Krauss at the University of Colorado, we determined that the A138T mice have approximately 2% of PCC enzyme activity. Unlike the original PCCA mice with no PCC activity, most of these A138T mice survive to adulthood, but have very similar elevations of the same blood metabolites seen in propionic acidemia patients. These include elevations in propionyl carnitine and methyl citrate as well as increases in glycine, alanine, lysine, and ammonia.

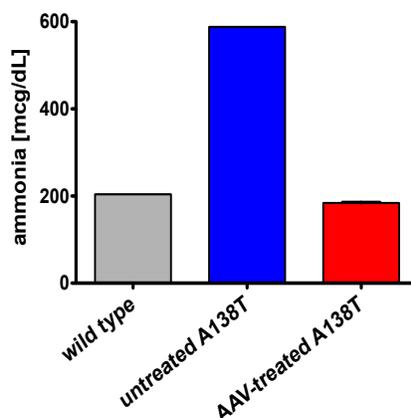


Fig. 1. Ammonia levels in normal mice, A138T PA mice, and treated A138T mice. Note: the ammonia testing method used here is different than that used in the clinic, therefore "normal" values may be different than typical reference values.

With this new mouse model, we were able to treat adult mice with adenoviral and AAV vectors expressing the gene for human PCCA. Both of these gene therapy vectors significantly reduced propionyl carnitine and methyl citrate levels in the blood of the mice within one week of treatment. The

AAV treatment also appeared to correct issues with feeding as the therapy resulted in significant increases in body mass just 1-2 weeks after injection. Additionally, propionyl carnitine and methyl citrate levels have remained low for over a year after treatment with a single dose of AAV and preliminary data suggests that A138T mice have much lower levels of ammonia as a result of treatment (Fig. 1).

These data suggest that gene therapy may be an alternate approach to liver transplantation for propionic acidemia.

In addition to providing a model to test new therapeutics, the A138T mice may also provide insights into the pathobiology of propionic acidemia. For example, knowledge of the mechanism by which PA affects certain organs such as the heart and brain is fairly limited. It is therefore notable that the A138T mice have increased

heart size and biomarkers suggestive of cardiomyopathy and perhaps arrhythmia. The mice may also have neurobehavioral symptoms that suggest some aspects of neurological features in PA patients. This may provide useful insight into the pathobiology of PA in humans.

Working together for a cure for PA!



The Propionic Acidemia Foundation Newsletter is designed for educational purposes only and is not intended to serve as medical advice. The information provided should not be used for diagnosing or treating a health problem or disease. It is not a substitute for professional care. If you suspect you or your children may have Propionic Acidemia you should consult your health care provider.

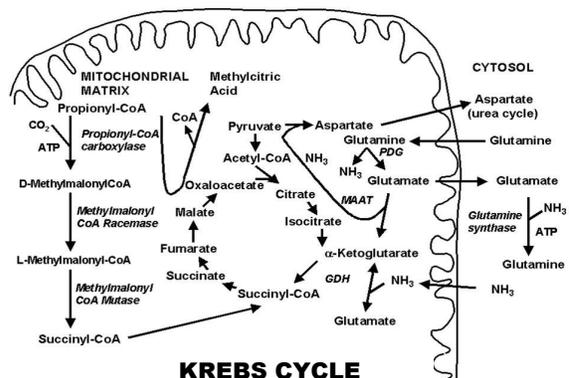
ANAPLEROTIC THERAPY IN PROPIONIC ACIDEMIA

Nicola Longo, Leisa B. Price, Eduard Gappmaier, Nancy L. Cantor, Sharon L. Ernst, Carrie Bailey, Marzia Pasquali.
University of Utah, Salt Lake City, UT.

Propionic acidemia is a rare metabolic disorder caused by a deficiency of propionyl-CoA carboxylase, the enzyme that converts propionyl-CoA to methylmalonyl-CoA. Patients with propionic acidemia cannot metabolize propionic acid, which sequesters oxaloacetate from the Krebs cycle to form methylcitric acid. This may lead to a deficiency in Krebs cycle intermediates.

The objective of this study was to determine whether adding glutamine, citrate, or ornithine α -ketoglutarate (anaplerotic agents that could fill up the Krebs cycle) to patients' diets affected plasma levels of glutamine and ammonia, the urinary excretion of Krebs cycle intermediates, and clinical outcome. Each supplement was administered daily for four weeks with a two week washout period between supplements. The supplement that produced the most favorable changes was supplemented for 30 weeks following the initial study period.

The urinary excretion of the Krebs cycle intermediates, α -ketoglutarate, succinate, and fumarate increased significantly compared to baseline during citrate supplementation, but not with the other two supplements. No significant changes in glutamine levels were observed with any supplement.

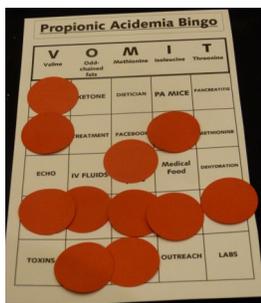


However, supplementation with any anaplerotic agents normalized the physiological buffering of ammonia by glutamate, with plasma glutamate and alanine levels significantly increasing, rather than decreasing with increasing ammonia levels.

Hospitalizations per year did not change during the trial period, but decreased significantly in the 2 years following the study (when citrate was continued) compared to the 2 years before and during the study. These results indicate that citrate entered the Krebs cycle providing successful anaplerotic therapy by increasing levels of the downstream intermediates of the Krebs cycle: α -ketoglutarate, succinate and fumarate. Citrate supplements were safe and might have contributed to reduce hospitalizations in patients with propionic acidemia.

PAF CONFERENCE (CONTINUED FROM COVER)

Finally, Dr. Kraus spoke after a break. He presented the "Approaches to Molecular Therapy for Propionic Acidemia." During this presentation, he explained the concepts behind chaperone therapy and discussed various ways that



substances could enhance enzyme activity in PA patients.

Afterwards, we played PA Bingo (otherwise known as VOMIT - Valine, Odd Chain Fatty Acids, Methionine, Isoleucine and Threonine) which was fun and educational as the boxes were filled with PA vocabulary.

I am glad I had the opportunity to volunteer at the conference. I found it enjoyable to hang out with individuals with PA and their families. Additionally, I learned a lot about biology through both the conference presentations and the lab tour. All-in-all, it was a valuable experience.



The conference was supported by VitaFlo and the Gene Team. It was attended by 7 families from the following states: Illinois, Missouri, New York, South Carolina and Colorado.

Publication Note: The PAF Newsletter is published twice a year. Readers may subscribe by writing to PAF, registering online or calling 877-720-2192. Letters and article submissions are welcome for consideration and may be sent to paf@pafoundation.com or mailed to Propionic Acidemia Foundation 1963 McCraren, Highland Park, IL 60035. If you would like to be removed from our mailing list or receive the newsletter via email, please contact us. We are deeply appreciative to Publishers Printing Company for donating the printing costs of the newsletter.

LUCY'S STORY

Hello friends,

My name is Lucy Harding and there are a lot of things that I do to contribute to this world even though I have Propionic Acidemia. There are lots of new things I just started doing this year and it has been unbelievable. It has created a whole new world for me.

I am 15 and a sophomore at HCHS in Lexington, KY. My favorite classes this year are child development and chorus. Last year my favorite class Algebra and I it was really hard for me but I still was able to get a B. This year I take biology, world civ, geometry and English. I have to have a teacher make sure I stay on task and sometimes write for me because I can't write quick enough to keep up. We do a lot of homework and mom has to drink a lot of wine to get through it.

I get help with making sure my tube feedings get done at school, I do them on my own but I still have an adult to make sure they get done on time. I take my lunch that mom and I decide on and measure at home. An adult makes sure I eat everything and if I eat something else, I call my mom to check and I bring home the package. At lunch you don't have to sit with your specific class anymore and you can sit wherever you want. I like going to school because I get to see my friends everyday. There are some people that make fun of me and are never going to change. My fishy smell is a big issue. When people bully me I try to go to the principal or the counselor. They try to help but kids don't always listen. Sometimes I get down in the dumps about this, but don't want to talk about it because they will call me a snitch.

This year the most exciting thing was starting special Olympics cheer leading. This has opened up a whole new world for me because I made a bunch of new friends. It is a very good sport to do with friends because we work as a team. We went to competitions in Atlanta and here in Lexington. We have the coolest makeup and this year we got new uniforms with lots of sparkles. We have one of the most well known special Olympics cheer teams and were undefeated for 11 years. We have lots of people who can do flips and handsprings. I can do a forward and roll, an OK toe touch jump and I am working on a cartwheel but am trouble with my arm strength and straight legs. Cheersport competition in Atlanta was amazing. We won second out of 13 teams in the Special Needs Elite Division and I got a Cheersport jacket because it was my first year. I was so excited about being up on that stage with my team. I told my mom it was the best day of my life.

Even though I am 15 my favorite hobby is to play with my American girl dolls. I have 18. I also have been doing dance since I was 3. I go to a church dance program with my friend Anna, but this year I

am going to stick to ballet and work with my elementary school dance teacher.

It feels like I've been able to eat this well since birth now. I really love to eat. Some of the things I eat are chips, pretzels, crackers, goldfish, strawberries, pineapple, apple, grapes, bananas, blueberry, tomato, mushrooms, cooked onions, cooked cabbage, corn, carrots, broccoli, beans, peas, edemame, sweet potatoes, pizza, pasta, french fries and my dad and I go get Chinese once a week (veggies and rice for me). I also drink things like water, juice, milk, and sprite. I don't drink my formula though because it tastes bad.

This year I was also in a Special Needs pageant where I won second in the talent part. I sang a song from a Barbie movie about friends and I sang acapella. I have a good voice and I like to sing. I went to Therapeutic camp this summer. I didn't get to do Riding for Hope with the horse park this year because we were too busy with cheer. I was taking a tumbling class until I had to have surgery on my umbilical hernia and I will start that back soon. I took a musical theatre class at the Lexington Children's Theatre one week this summer. It was called "Show your Wicked Side and we sang lots of songs from Wizard of Oz, Wicked, and The Wiz. I sang a solo part in Easy on down. After that we went to Chicago the first of August for a Special Olympics Gymnastics camp. It was great but really wore me out. Mom has been worried about me ever since we got back because I have been taking lots of naps. Dad says I need more exercise and they are making me take lots of walks and bike rides. The best part was I got to go to the American Girl store and have dinner.

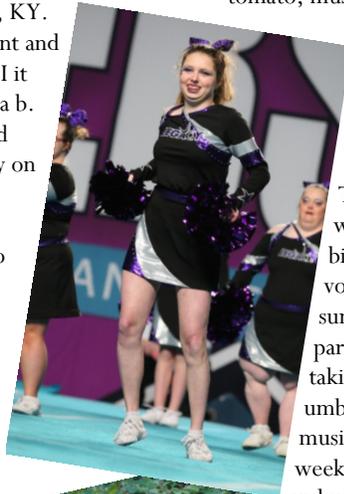
I have a CLS worker who started in March. Her name is Miranda and she makes me do a lot of chores. We go to the grocery and she makes me estimate costs and choose which brand to get. I always get the cheapest.

We exercise, cook, run errands, go to the library, do laundry, work on reading comprehension, go shopping at the mall and she makes me count out the money. We had a yard sale and I sold all my barbies so I could make money for Chicago. Miranda made me add up the sales and count out the change. Even though she makes me work I like her and we do fun things too like watch movies, have brunch with her niece, and get manicures. This summer she helped me learn to wash my own hair. I figured out I could wear my goggles in the shower and the water wouldn't get in my eyes. That is really great!

I am back in school now and Cheer starts again next week. We are really busy with all this and mom says it wears her out, but it is fun! That's about all I have to tell for now.

Love – Lucy

ps. I love to text and email so send me a message sometime. My phone number is 859-229-0744 and I just use my mom's email – jharding@twc.com



LUKA'S STORY

Luka was born September 14th 2011 and we were sent home on Friday September 16th. Within hours of having him home, we became concerned with his lack of interest in eating, irregular breathing patterns and overall lack of response to stimulation. On Saturday 9/17 we took him to the walk-in to see a pediatrician who immediately arranged for an ambulance to take him to St. Marys hospital in Madison. Almost simultaneously, his newborn screen came back



indicating that he had some type of metabolic disorder. Things were happening extremely fast. Before transferring him to the American Family Children's Hospital (AFCH), Luka was baptized and many prayers were shared. Upon arrival to the AFCH, Luka was put on dialysis and many intrusive lines were placed. His ammonia level was 800, had uncontrolled hypotension, seizures, respiratory hypertension... it was overwhelming to say the least. Sunday evening, he had a respiratory hypertension crisis' that drew the whole staff into his room as they struggled to figure out how to 'bring him back'. Miraculously they pulled him out of that mysterious 'crash' and he started to improve, slowly. I remember feeling for days after, that it felt like we were all 'chasing our tails' with everything he had going on medically. By September 19th, our Geneticist had shared that he thinks Luka was "through the hurricane, but that there were rough seas still ahead". It was at this point that my husband, Ryan, placed a sign on Luka's hospital door that said, "please say something positive to Luka before exiting!". It seems simple, but it ended up to be so powerful. By the 20th Luka was officially diagnosed with Propionic Acidemia. Luka's Geneticist, Dr. Gregory Rice is like a superhero in our house. He confidently lead the entire medical team in making decisions for Luka while gracefully educating our family and explaining each step along the way. There were good days, and bad days during our stay at the children's hospital.

October 12th we arrived home with our beautiful baby for the 2nd time.

Luka's first year of life was, to say the least, turbulent. About every other month we were hospitalized with some sort of 'Fluka' as we called them that either started with acidosis or inevitably lead to an acidotic, very sick child. In order to keep Luka metabolically 'stable' we discovered that Luka needed to be significantly overfed. He very quickly gained a lot of weight and was frequently vomiting. July of 2012 we found ourselves rushing a vomiting child to the hospital again. We were surprised when the Geneticist told us that he thought Luka was a candidate for a liver transplant. We remember it being mentioned in the hospital when he was first diagnosed, but at that time, it was a 'worse case scenario' decision that didn't apply to Luka. Dr. Rice had presented Luka's case to several other doctors who specialize in working with metabolic disorders, specifically PA and were all in agreement that they would suggest a transplant for his case. As a family, we did think very carefully about the decision, and felt confident in Dr. Rice's recommendation. We couldn't imagine what Luka's life would be like if we continued with the pattern he

had shown in his first year of life. Luka was put on the transplant list and we entered the 'waiting game'. For months, my stomach would turn each time the phone rang until we got the call and he received the transplant on October 26th 2012. By the next day, his ammonia level had dropped to 40 (his 'normal' before that was 80) and no ketones. On November 2nd, the geneticist brought us a print out of Luka's amino acids. He suggested we frame the sheet because all of the amino acids were in

the normal range... something that had never happened for him before.

One of the first things we noticed about Luka when we got home after the transplant was how 'alert' he seemed. We didn't realize it before, but it was almost as if a fog had lifted and he was experiencing a version of the world that was so much more vivid and sharp. The fridge would make a sound and he would turn his head quickly as if he had never heard that sound before. He also seemed more engaged with each of us and purposeful when he played with toys.

As Luka continued to recover from the transplant, it was time to start talking about how to gradually introduce food. There is no 'prescribed' approach to this, so we worked together with the team to determine how to allow Luka to become hungry while giving him sufficient calories and protein via his g-tube to make sure he stays nourished and stable.

Luka has come such a long way since the transplant. He has started to eat certain foods orally (his favorites are spaghetti, gerber cheese puffs, apples and hot dogs). Just this week (August 14th) we cut back his formula to allow space for protein and calories to come from food for the first time. He is allowed 5 grams of protein orally with the goal of moving towards 10 gms, then 15 within the next few weeks. As he eats more orally, we will taper the pediasure we mix in his formula accordingly. Eventually, the hope is that he will receive the majority of his nutrients from food orally, and then supplement with propimex-1.

Luka has been hospitalized a couple of times since the transplant. What is significantly different about these hospitalizations is that he has remained metabolically stable each time. We adjust his diet to a 'sick day diet' just in case and he is still treated as a patient with PA; however, Dr. Rice is very pleased with how well Luka is doing metabolically.

Developmentally, Luka is doing exceptional. He is so much more active since the transplant. Physically, he is walking, starting to run a bit, going up and down stairs independently and jumping. He is not talking but has really appreciated learning a few signs to use when communicating with us. He will be turning 2 next month, but is the size of most 3 or 4 year old children. He loves to read books, vacuum, and find people's ears. Luka is the best cuddler and he spreads love and smiles everywhere he goes. We are so blessed to have him in our life.

-Malory and Ryan (and Luka)

PAF FUNDRAISING SPOTLIGHT

PAST EVENTS AND CAMPAIGNS

- 4/2013 - **Wingfest**, Milwaukee, WI - \$1000
- 6/2013 **SPEX Company BBQ**, Aberdeenshire, Scotland (below)
- 8/2013-? (ongoing) **Hike for Maren and PAF**, Colorado
- 9/2013 **8th Annual Tailgate Party & Corn Hole Tournament**, Gahanna, OH, GwenForACure.com (right)

DONATIONS IN MEMORY- over \$9100

- Connor McKillop (bottom)
- Leonard Keller - Jordan Franks's great uncle
- Mary Oberschlake - Hogan Koehl's great grandmother
- Michael R. Popowicz, Brett Young's grandfather



SPEX Company BBQ

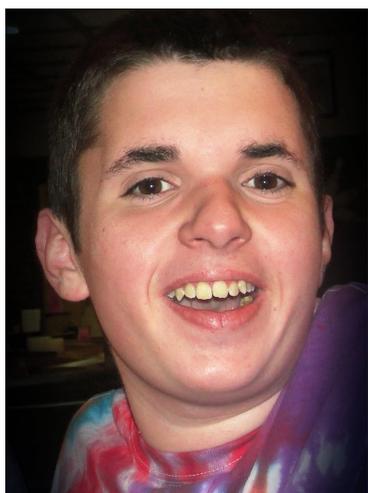
On the 22nd June 2013 saw SPEX Services, an oil service company, hold a company BBQ for employees and their families within the grounds of the owner's home at Dunecht House, Aberdeenshire, Scotland. The location and entertainment were fantastic, with everything from absailing walls, childrens rides, face painting, live music and much much more.

Good friends of mine, Roselyn and Stephanie Eadie work for SPEX and earlier this year they nominated PAF as the company's 2013 international charity. The employees have been raising funds for three charities, including PAF through a variety of events. At the BBQ raffle tickets were sold and they raised £275 (\$400) for PAF.

It was a great day (apart from the rainy weather) and I would like to thank everyone at SPEX for their generosity.
-Ruth Milne (Eilidh Duncan's Mum)



CONNOR'S TRIBUTE



Connor William McKillop July 2, 1992 - June 25, 2013

Connor was known to many as a happy person who always shared his love for living with others. Whenever Connor was around his smile was contagious. He could always make others laugh with his movie impersonations and talks of his favorite television shows. From movies like Big Daddy to shows such as Legends of The Hidden Temple, Connor was able to share his love for good television. Connor loved school and all of the people he was able to see on a daily basis. He worked in his High School's school store and would attract people just to stop and chat with him for a while. Connor was also known to throw some amazing birthday parties. He would make sure that everyone was involved and wearing a common theme t-shirt to participate in his special day. He was just so happy to have all of his family and friends together with him. Relationships were the most important part of life to him. His family and friends were his world. Even if Connor didn't come out and say it directly, he showed us through action that you must keep family and friends close through good times and bad. Connor has touched a countless amount of people in his short 20 years of life. His infectious laugh can still be

heard in all of our hearts and he will continue to live in our memories forever. Connor McKillop did not win the genetic lottery. But he did win the parent lottery, the brother lottery, and the extended family lottery. Connor came into the world with the cards stacked against him, forced to play a hand that many kids could not win, and yet ... through resilience, and love, and support, and grits, and guts ... he lived 20 of the best years a person could possibly live.

PAF ANNUAL REPORT

FINANCIAL REPORT

Revenue:

Contributions: \$78,446
 Interest Income: \$152
 In Kind Donations: \$2,104
Total Revenue: \$80,702

Expenses:

Research Grants/Registry: \$88,098
 Programs & Outreach: \$4,895
 Printing (in-kind): \$2,104
 Fundraising: \$1,020
 Operational Expenses: \$1,066
Total Expenses: \$97,183
 Cash Assets 8/1/2012: \$133,851
 Cash Assets 7/31/2013: \$117,370

BOARD OF DIRECTORS/OFFICERS

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Board disclosure: Jill Chertow Franks is the sister-in-law of Michael Rosenson.

Donations made by board members totaled \$1,140.

PROGRAM ACCOMPLISHMENTS

Research: Grants Disbursement:

- \$27,000 Marisa Cotrina, Ph.D. University of Rochester, Rochester, NY : "The impact of pa on brain astrocytes: an in vitro model to test mitochondrial therapy in PA"
- \$5,000 Holmes Morton, M.D. Clinic for Special Children, Strasburg, PA "The Biochemical Basis for Keto-Acidemia, Encephalopathy, Metabolic Strokes, Heart Failure and Long QTc, and a Discussion of Current Therapies" workshop
- \$21,200 Loren Pena, M.D., PhD, Duke University, Durham, NC "A prospective study of biochemical parameters reflective of metabolic control in propionic academia" in PA"
- \$28,898 Sarah Venezia, M.S. and Jan P. Kraus, Ph.D., CDHSC Denver, CO: "Enzyme Replacement Therapy for Propionic Acidemia"

Outreach:

- Distributed fall and spring newsletters to affected families, clinicians, and donors
- Attended PA Workshop at Clinic for Special Children, Strasburg, PA
- Held PAF Education Conference in conjunction with Children's Hospital Colorado, Denver, CO



We want to hear from you! Have a PA story to tell, event to promote or news? Spring newsletter submissions due by February 28!

Help Us Find the Cure!

Name _____

Please send an acknowledgement to:

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Name _____

City, State, Zip _____

Address _____

Phone _____

City, State, Zip _____

E-mail _____

Enclosed is my contribution of \$ _____ in honor of/in memory of _____

If you work for a company that has a matching program, please include the matching form.

Please mail your check made payable to: Propionic Acidemia Foundation 1963 McCraren, Highland Park, IL 60035

Thank you for making a difference.

SEARCHING FOR A CURE
HOPE FOR OUR CHILDREN

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volunteers and we couldn't
do it without you

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