SEARCHING FOR A CURE HOPE FOR OUR CHILDREN

Propionic Acidemia Foundation

VOLUME 1, ISSUE 16 SPRING 2014

National Institute of Health MINI Study

written by Jill Chertow Franks

We heard about the NIH MINI Study: Metabolism Infection and Immunity in Inborn Errors of Metabolism last year and contacted Janet Shiffer for more information. The cost of our flights, stay at the Children's Inn, appointments, and food was covered by the study.

On Monday, March 31st, we boarded a plane to Reagan National Airport. Upon arrival we were picked up and taken to the NIH Campus in Bethesda Maryland and checked in at the Children's Inn.

On Tuesday morning, we walked over to NIH (you can also take a shuttle) to register and then met with Dr. McGuire and Janet Shiffer. We went over our schedule for the two days we were going to be there and they answered our questions. They even scheduled some additional consults at our request. Each schedule will be based on you or your child's needs and discussions with the MINI team. We had a very busy two days with lots of consults including Nutrition, GI, OT, Speech, PT, and a Physiatrist in addition to an EKG, Liver scan, blood draws (one each morning), Hepatitis A Vaccination, and an attempt at a DEXA scan. I realize this sounds like a lot, but it went extremely smoothly and Janet kept in touch with text messages and stopping by at our various appointments.

Jordan is 14 and has seen many specialists for years and we were very impressed with all of the specialists we met with and will be using their suggestions and information. We flew

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PA Family Day

September 20-21
Columbus, Ohio

paf@pafoundation.com
Registration form on pg. 8

In conjunction with 9th Annual Tailgate Party & Corn Hole Tourney
(see pg. 6)

INSIDE

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.

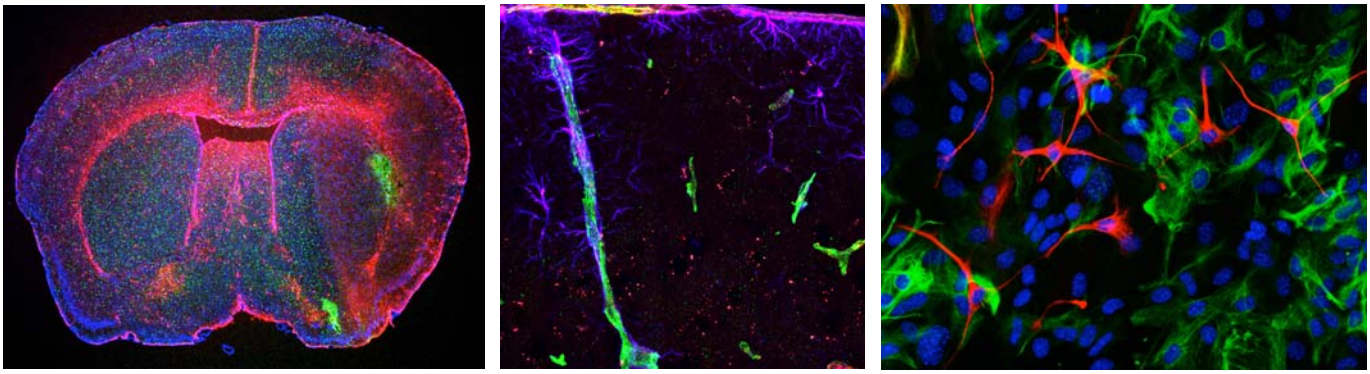
VISION: To create a future where Propionic Acidemia can be prevented and any affected individual can be cured and live a productive life.

IMPACT OF PA ON BRAIN ASTROCYTES

PAF project: Impact of propionic acidemia on brain astrocytes: an in vitro model to test mitochondrial therapy in PA.

P.I. Maria L. Cotrina, PhD.

Propionic Acidemia (PA) affects every cell in the body, but it has particularly nasty effects in the brain. Despite the profound damage that the disease causes to the nervous system, published research has largely neglected to study how the brain manages the build-up of toxic compounds produced by PA patients. This is a key issue, especially in light of the current trend of performing liver transplants as therapy for PA patients.



A mouse brain slice (left) shows different markers for brain cells: astrocytes in red, immune cells in green, cell nuclei in blue (all cells). There is an infarct (stroke) in the right side of the section, hence the colors change respect to the left side because the cells react to the injury. Astrocytic processes (purple) wrapping a blood vessel (green) in the brain (center). A culture of brain cells that shows neurons (red) surrounded by astrocytes (green) and other cells (blue) (right).

It is important to establish whether the damage that the brain experiences in the disease results from toxic compounds produced within the brain or from toxic build-up in the rest of the body that then reaches the brain. In the first case, liver transplantation would likely not correct the deficits produced by brain because the brain will continue producing toxic metabolites regardless of what happens to the rest of the body. If, on the contrary, the damage to the brain is produced because of the very high toxic metabolites that accumulate in the blood that then enter the brain, lowering the amounts of these toxic molecules (a consequence of liver transplantation) should help to preserve brain function too.

Using mice genetically engineered to carry one of the mutations that cause PA, our studies aim to decipher how brain cells react to the chronic effects of PA. We particularly focus on a type of brain cells named astrocytes. Astrocytes belong to a group of brain cells called glia that work as support cells for neurons; they eliminate metabolic waste and toxins (including ammonia) in brain and participate in the production of natural antioxidants. They also contribute to brain volume regulation and to the clearance of neurotransmitters (the signaling molecules released by neurons) after brain activity.

The way astrocytes can perform all of these functions is because of their unique organization in the brain: astrocytes establish numerous contacts with neurons and their connections, and they are also in intimate contact with the blood vessels that supply nutrients to the brain. This particular architecture of the brain enables astrocytes to perform their functions very efficiently as they are the very first cells that get in contact with the nutrients that come in from the blood and with the toxic metabolites that the blood may carry, including high ammonia, which is often involved in PA pathology.

Astrocyte function is impaired in many neurodegenerative and neurological disorders, such as Alzheimer's disease, Parkinson's disease and Amyotrophic Lateral Sclerosis. These facts strongly argue for a possible role for astrocytes in the pathology of metabolic diseases, including PA.

(continued on pg. 3)

LAB PARAMETERS REFLECTIVE OF METABOLIC CONTROL

Update on "Laboratory parameters reflective of metabolic control in individuals with propionic acidemia" Duke University

We recognize that the scant information available on how we can use standard laboratories to guide treatment in PA can limit our ability to care for affected individuals. The overarching goal of the study titled "Laboratory parameters reflective of metabolic control individuals with propionic acidemia" study is to begin to address this issue.

The aims of the project are to develop an assessment tool for metabolic status in PA utilizing readily available laboratories, and to assess the usefulness of several exploratory biomarkers to determine metabolic status in PA. We are comparing the values of these labs during times of health and in illness.

The study was launched in the spring of 2013, and we are excited to report that recruitment has been very successful so far. Participation requires submitting blood and urine samples along with specific medical information to our laboratory during regular clinic visits and during illness.

Thank you for your support of the study – we could not do it without you. Additional information can be obtained through the PAF website or by contacting the study coordinator, Jennifer Goldstein, at jennifer.goldstein@duke.edu.

Propionic Acidemia International Patient Registry Update

Launched September 2012, 38 people have completed the survey. The PA Registry provides a way for PA patients and families worldwide to improve the understanding of the disorder and accelerate research by reporting information about how the disorder affects them.

The Registry is itself an IRB-approved research project and the data collected will help characterize the condition of people living with PA. Please go to www.paregistry.org for more information and to begin the process. If you have already registered, please update any changes.

IMPACT (CONTINUED FROM PG. 2)

The experiments in this project aim first at screening for genes that are expressed differently in astrocytes from our PA genetically modified mouse compared to the healthy mice. To do this, we are first isolating the astrocytes from the rest of the brain and then looking to establish if there are any genes that differ between the PA and healthy mice.

Secondly, we are analyzing the astrocytes directly in the brain of the PA mice, without isolating them, so that all their interactions with the rest of brain cells are preserved. In order to do this, we cut very thin sections of brain tissue and stain them with different markers that enable us to identify astrocytes in contact with blood vessels or with neurons. At the same time, we are also studying how the rest of the brain changes in structure or properties in the PA mice.

Last, as damage to mitochondria (the energy suppliers of the cells) seems to have a prominent role in a wide range of brain diseases, and propionic acidemia causes clear defects in mitochondrial function, we plan to test the efficacy of antioxidants in astrocytes in culture (isolated from the brain and grown in a dish in the laboratory).

With all of these approaches we aim to get more knowledge about how brain cells are affected by PA but also to improve survival and function of PA-affected astrocytes and, by extension, of brain function in PA patients.

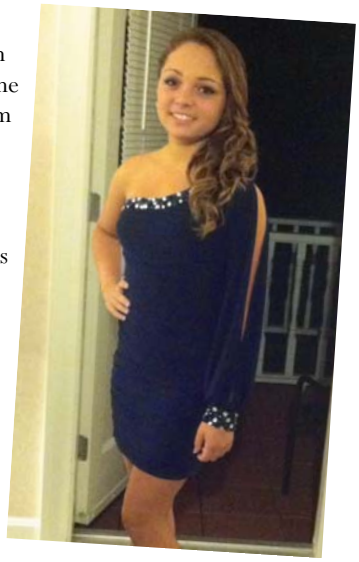
Publication Note: The PAF Newsletter *is published twice a year. Readers may subscribe by writing to PAF, registering online or calling 877-720-2192. Letters and article submissions are welcome for consideration and may be sent to paf@pafoundation.com or mailed to Propionic Acidemia Foundation 1963 McCraren, 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.*

GABRIELL'S STORY

Hi, My name is Gabriell and I was born in Taunton MA on October 10th 1999. I was diagnosed with PA at birth through the newborn screening. I live a pretty normal life! I am currently a 9th grader at a great school. I now live in Fryeburg Maine with my parents and my younger sister. I love to dance and I currently am on the Act One Dance Companies competitive dance team! I also ski, play softball, soccer and really enjoy hanging out with my friends!

I didn't always live so normally. I was in and out of hospitals the first 10 years of my life. I had everything from just a virus to scarlett fever and everything in between. I have always been on a low protein diet but i didn't start any medication until I was 5. I am very small (4'11) and sometimes kids say hurtful things, but I remember my mom always telling me "great things come in small packages", plus my family and friends love me the way I am! When I was 5 I started on carnitine.

When I was 11 I started on my protein replacement formula. I hate it but I know I have to drink it. I don't have any learning disabilities, heart problems or any other severe medical complications that go along with having PA. I am very grateful to have had the care from my parents and doctors to keep me healthy all these years! I love them all tremendously, and couldn't have done his without them!



I do worry about my future, but I'm very grateful to have lived this long with only a few hiccups along the way! I will continue to live my life in the moment a cherish each relationship, friendship and learning experience I encounter! I pray one day there will be a cure! Thank you for all the research everyone does!

Sincerely,
Gabriell,14, PA

NALANI'S STORY

My daughter Nalani Johnson just turned 14 years old!! Things are going great with her lately so I thought I would write an update. She is in 8th grade and loves school. Every morning she wakes up asking if she can go to school even on the weekend. Next year for high school I am planning on sending her to a self-contained high school instead of the public high school in our district. I think this will be better for her socially and she is so tiny (4ft 9in) I am worried that the high school will swallow her up.

At her school they just started a cheerleading activity that we are very excited about. Nalani is currently in a Basketball class that is run by physical therapists that she loves. She is also participating in a dance class. One of the best things we have done is the Miss Amazing Pageant-LOTS OF FUN!! She also recently received a new adaptive bike from the St. Louis Variety Children's Charity, we are really looking forward to riding it! She has a speech therapist in the evening and a tutor.

Nalani has a speech therapist, Pam that we love! We have been seeing her for about 9 years. She has at home tutors, Ann and Hope that have been WONDERFUL. Ann was a teacher that Nalani had in grade school. She attends our IEP's with us and helps with what to ask and what the school should be doing. One thing I regret is that I was not more involved with Nalani in her early education. She had so many hospitalizations and medical hurdles that I was more focused on her health and not her education. I have always had therapist that come out to the house to work with us, and her teachers were great so I knew she was in good hands but, now it seems like I am struggling on how to handle things with her education.

Metabolically recently things have been so much better!!! She was running a 100+ ammonia levels for years and after changing to Peptamen Jr. her last 3 of 4 ammonia levels have been in the normal range!! This is huge for her, those ammonia levels kept me up worrying at night. Constipation has been another problem she has had. I have been doing my best to stay on top of this, because it seems like that is key to keeping her from developing ketones and vomiting. She is fed by g-tube still, she eats a little by mouth her favorites are lemon pudding, salty chips with salsa and onion rings. Echo's have been normal and seizure free for 6 years now. She sees Orthopedics for a curve in her spine. We have chosen to put her on birth control because she had been getting very unstable at times. Allergies were also an issue. 2 years ago she got a type of sedated Lasik surgery, so she no longer wears glasses. She is just now losing the last of her baby teeth so we are going to talk to the Orthodontist about what can be done to help her speech. I think this will be our next hurdle.

Nalani is at around a 4-5 yrs old level as far as speech but, she reads at a 3-4th grade level. Math is very difficult for her she is working on using a calculator but, does not have a real concept of quantities. She LOVES to read and play on her Ipad! She is on Propimex 2, Peptamen Jr and I give her some of her protein by foods I have blended up in the Vitamix. Her meds are Phenobarbital, Citra K, Carnitine, Flagyl, Miralax, L-alanine, Valine, and Nasonex.

Nalani is a wonderful daughter, a terrific big sister and truly a remarkable person!

Kristin's Story

Kristin, it's hard to believe it's been fourteen years since you were born. Texas did not screen for propionic academia in 1999, and we found that out the hard way when you were five months old. Your first metabolic crisis landed our family in the ER on your brother's third birthday, but at that time the physicians only thought you had a virus. After three days of IV fluids and glucose they sent us home. We still did not know you had PA at that point and continued to feed you high protein Similac. Over the next week you started to go downhill again with a lack of emotion, staring into space, and continued vomiting. By the time you were rolling your head back and forth your pediatrician called and told us you had PA. Fortunately the ER physician who examined you had ordered organic acid tests 10 days prior or we still would not have known what was happening to you. I guess that started the most difficult journey your dad and I could have imagined.

When we brought you home from the hospital you were limp, emotionless and had no upper body strength. You had lost your ability to lift your arms, your head was unsteady like a newborn, and you flopped over at the waist. Your skin was very pale, and the mental connection I had formed with you was gone. I did not know who you were anymore. I had lost my daughter, and I did not know if you would ever come back. That's a hard thing to look at, day after day. But over time, with a lot of patience, therapies and normal playing, you have grown into a very pretty young lady who can do a lot of things that we initially thought you might never do. Although you do not walk, you crawl or knee-walk everywhere in the house, play with puzzles, musical toys and instruments, your mini computer and communication device, and you love singing songs with anyone. You have now confiscated most of your brother's old toys, and your most fun games these days are zooming trucks or hot wheels cars across the floor with someone, or swinging your Star Wars light saber around! Your favorite shows continue to be Clifford, Little Bear, Zoboomafoo and Veggie Tales. You love to go outside, go for rides in the van and play on the piano. Your favorite DVD concert is U2 with Bono singing Beautiful Day. You will stand on your knees in front of the screen with a big smile on your face and then pull your shirt up over your head and sing when Bono comes on stage. My goodness, if you were "normal" I might have a wild child on my hands with you turning into a teenager!

Over the years your PA diet and meds have changed quite a bit. You are no longer on the anti-diuretc hormone DDAVP because we found out, again the hard way, that you did not have diabetes insipidus. That was a wrong diagnosis at age 4 and somehow for six years you managed to do well on a drug that could have killed you. At age 10 you started to have seizures and everyone was puzzled. You never had seizures in the past. Finally, we realized you did not have enough sodium in your diet and after some testing it was determined your kidneys worked fine and you did not need DDAVP. You really shocked the doctors with that one. One doctor said you are an enigma wrapped in a mystery inside a puzzle box! You still take a number of nutritional supplements which are designed to help ease oxidative stress or increase energy production. Theses include B complex vitamins, high dose biotin, Co Q10, vitamin E, sodium succinate and L-carnitine. We also give you vitamin D3 and extra calcium.

Your once tailor-made g-tube diet that for years included Gerber veggies, fruits and cereal was replaced a couple of years ago with a synthetic formula mix of Propimex-2, Prosobee and Polycose. This diet was supposed to simplify things , but instead it has complicated your care. In addition to gaining more un-needed weight, your new diet has made your skin look paler unless we manage to get you outside in the sun a lot. You were more stable on your old diet that contained a complex carbohydrate (oatmeal) than the new diet that contains Polycose or Sol Carb. I'm sure your glucose was maintained at a more even level with oatmeal than a simple sugar that causes your glucose to spike every 2 hours when you are bolus-fed during the day. The main problem is that to keep you stable and ketone free we've had to add more calories than we'd like and you have gotten quite heavy. You have always gained weight easily, but this synthetic diet has caused you to gain the most. Another problem that has developed more as you've gotten older is that any increase in protein requires an increase in calories or you're sick. It's kind of ironic that at age 14 we understand you so much better, but that it takes more tinkering with your diet to keep you stable. Perhaps this is a companion of puberty?

Well, Kristin, you are now a teenager, and we are moving into another black box, a real unknown. I hope you continue to stay stable and happy once the hormones really start to cycle. And I hope you adjust well to your brother moving off to college in a year or so. You love your brother so much! What are your dad and I supposed to do when Eric is not here to say "nite-nite Kristin!" as your sign-off to go to bed? You already need Benadryl and melatonin to sleep well. We might have to do Face Time! Sweet dreams pumpkin, we love you.

PAF EVENT & FUNDRAISING SPOTLIGHT

UPCOMING EVENTS AND CAMPAIGNS

- 5/4/2014- **Blue Cross Broad Street Run, Philadelphia, PA** Team Bretty Bunch from Milliman Philadelphia will participate in the Blue Cross Broad Street Run raising money and awareness for the Propionic Acidemia Foundation. The Blue Cross Broad Street Run course is a 10-mile run through several Philadelphia neighborhoods along Broad Street. The Bretty Bunch is named in honor of Brett Young. (see photo below)
- 9/20/14- **9th Annual Tailgate Party & Corn Hole Tournament for PAF, Gahanna, OH,** GwenForACure.com
- 9/20-21/14– **PAF Education Conference**, Columbus, OH (see registration form pg. 8)

PAST EVENTS AND CAMPAIGNS

- 1/2014- **Young Family Superbowl**, Pennsylvania, $1000+
- 1/2014- **Branch Family Superbowl**, Indiana, $500+
- 1/2014- **Lincoln Financial Distributors "Jeans for a Cause"**, Radnor, PA, $675
- 3/2014- **McKinley NCAA Bracket Challenge,** Kentucky $430
- 3/2014- **TGBK Dine Out Fundraiser** - Illinois, $3500 total, $925 to PAF - This year we decided to have a dine out fundraiser. We set up a March calendar and the following restaurants gave a percentage of that night's food sales to our charities. Thank you to California Pizza Kitchen, Tony's Subs, Il-Forno's, Claim Company, Tom and Eddies, Chipotle, Trax, and Pot Belly.

DONATIONS IN HONOR

- Brett Young's birthday
- Angelica Stageman's 5th birthday
- Maren Stecken's 2nd birthday
- Ben Sweetman

DONATIONS IN MEMORY

- Carla Lenert Boyd
- John Dawe
- Virginia Houdek-Martin
- Nicholas Phillips
- Bob Phillips

Dear PA Family,

Our son, Reuben, celebrated his 30th birthday March 22nd. In lieu of gifts, we suggested a donation to the PA Foundation. We have such incredible friends, family/ church family, many of whom decided to give a donation and a gift. Please accept this $410 in honor of Reuben. He is such a gift and a blessing to us. Thanks for all you do!

The Kleckleys
Patt, Wade, Adrianna & Reuben

NIH MINI STUDY (CONTINUED FROM PG. 1)

home on Wednesday, April 2nd.

I will be speaking with Dr. McGuire in a couple of weeks to go over Jordan's labs. As part of the study, we consented to giving Jordan the Hepatitis A vaccine and plan to return to NIH next month to follow up.

The Children's Inn was an amazing place with lots of activities including an incredible playground, learning center, arts and crafts room, teen room with air hockey, pool table, and video games, There was even a class on healthy snacks, an exercise class and a workout room. Dinner was brought in and served by a group for one of the nights we were there and they had two large kitchens stocked with food that we could prepare for meals. They had fresh fruit and bagels in the morning and snacks out at different times during the day.

It was an incredible experience. Jordan was the first individual with PA to participate in the study. In addition to helping add to research on propionic acidemia, we received a lot of valuable information to help with Jordan's care. I would highly recommend looking into the study to see if it is something in which you would like to participate and would be happy to share more details about our experience. The cost of our flights, stay at the Children's Inn, and food was covered by the study.

For more information on the NIH MINI Study, go to http://www.genome.gov/mini/ or contact Janet Shiffer, C-RNP by phone at 301-451-9145 or by email at minstudy@mail.nih.gov

For more information on how you or your child can participate in research, please email research@pafoundation.com

Study overview: Infections play a significant role in precipitating life-threatening acute metabolic crises in patients with inborn errors of metabolism (IEM). At the present time, the medical community does not completely appreciate the status of the immune system in patients with IEM. Dietary complications or even the underlying enzyme deficiency can affect the immune system and its ability to fight off infection.

We hope to recruit interested IEM patients to study their immunologic status, including whether or not they have developed immunity to childhood vaccinations.

We want to hear from you! Have a PA story to tell, event to promote or news? Fall newsletter submissions due by August 1!

Help Us Find the Cure!

*Name*_____

*Address*_____

City, State, Zip _____

*Phone*_____

*E-mail*_____

Please send an acknowledgement to:

*Name*_____

*Address*_____

*City, State, Zip*_____

*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.

PAF Family Day Registration Form

Saturday/Sunday, September 20-21

Columbus, OH

Please complete the form below and email to paf@pafoundation.com or mail to: 1963 McCraren Rd., Highland Park, IL 60035.

1. **Personal Information**

   Name:

   Address:

   City: State: Zip Code:

   Email Address: Phone:

2. **Names of children attending with you**:

   Child's Name: Age: PA? Yes No

   Low protein meal needed? Yes No Allergies? Yes No If yes, specify:

   Child's Name: Age: PA? Yes No

   Low protein meal needed? Yes No Allergies? Yes No If yes, specify:

   Child's Name: Age: PA? Yes No

   Low protein meal needed? Yes No Allergies? Yes No If yes, specify:

   Child's Name: Age: PA? Yes No

   Low protein meal needed? Yes No Allergies? Yes No If yes, specify:

3. **Others attending**:

   Name: Relationship:

   Name: Relationship:

   Name: Relationship:

   Name: Relationship:

4. **Total number attending**:

5. **Is this your first PAF event?** Yes No

6. **Are you interested in signing up for the Corn Hole Tournament?:** Yes No

   Team Name:

7. **Are you a professional or vendor attendee? Yes No**

There is no charge to attend. Thank you and we look forward to seeing you!

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PROPIONIC ACIDEMIA FOUNDATION

PAF VOLUNTEERS AND BOARD MEMBERS ARE NEEDED!

PAF@PAFOUNDATION.COM

Propionic Acidemia Foundation is run 100% by volunteers and we couldn't do it without you

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