

# Propionic Acidemia Foundation

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## SMALL STEPS ADD UP TO BIG LEAPS IN RESEARCH... YOUR PARTICIPATION IS VALUABLE !

Research studies, both clinical and bench, are crucial for the advancement of our knowledge of disease. When you choose to participate in a research study, there is always the consideration of risk and benefit. One of the cornerstones of research studies with human participants is minimizing risk while maximizing benefit. As you consider participation, or your child's participation, in a research study, we often discuss that there is no promise of a direct benefit. This means that we cannot guarantee that the participant will have a benefit from participation. This kind of study may be a clinical trial or another type of study.

Regardless of the lack of a direct benefit, participation in a research study is immensely helpful for the investigator to derive new knowledge about the disorder, which is critical in moving the field forward. In the case of rare disorders such as propionic acidemia (PA), participation is crucial as there is strength in numbers. Available information on initial presentations and long-term complications in a large group of patients with PA is of paramount importance to have a wide scope of knowledge about the disorder. This knowledge also helps us to understand why some patients with PA have specific complications such as cardiomyopathy, pancreatitis, and renal disease. Although sometimes it feels like advancement is slow, every little step counts. -Loren del Mar Pena, MD, PhD



### IN MEMORY *Angelica E. Stageman*

*A challenging medical journey and a full loving life.*

*Her faith, courage and strength are an inspiration.*

*May her memory be eternal.*

*October 20, 2008-July 30, 2015*



## PA International Patient Registry

Help move research forward for propionic acidemia.

Participate in the Propionic Acidemia International Registry.

As of October 1st, there are 42 participants. For more information on joining the registry or to update your information, go to [www.paregistry.com](http://www.paregistry.com)

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**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.

## BARRY LAB UPDATE

We developed an adult mouse model of PA to test proof of principle for gene therapy and to delve into the biology of the disease. In this model, a partially active *Pcca* (A138T) gene from a PA patient replaces the function of the normal mouse PCC. We have shown that the A138T mice have only 2% of wild-type PCC enzyme activity, survive to adulthood, but have many symptoms that mimic those observed in PA patients including: elevations in propionyl-carnitine, methylcitrate, glycine, alanine, lysine, and ammonia as well as indications of cardiomyopathy. We have also demonstrated that intravenous gene therapy with adenovirus and adeno-associated virus (AAV) vectors reduces propionyl-carnitine and methylcitrate levels in the blood of the A138T mice. Notably, within a week of this gene therapy the animals are able to feed on normal protein-rich food resulting in substantial improvements in body weight. Long-term follow up 1.5 years after treatment demonstrates that single AAV therapy mediates significant reductions in systemic metabolite levels.

With continued support by PAF, we have explored 1) cardiac disease in PA mice and the ability to correct this by gene therapy, 2) effects of the disease on the immune system, and 3) are analyzing if the animals have neurological manifestations due to propionyl CoA carboxylase deficiency.

**Cardiac Symptoms and Correction by Systemic Gene Therapy.** We have previously shown that A138T mice have some degree of cardiac hypertrophy. To characterize this further, we evaluated cardiac metabolic profiles and cardiac structures in the A138T mice. Electron microscopy (EM) showed large structural defects in mice with the highest levels of PA metabolites. Surprisingly, all of the animals also had lipid droplets within their cardiac tissue as well as elevations in cardiac and plasma triglycerides and intracardiac propionylcarnitine. Echocardiography

revealed thinning of left ventricle walls and increases in internal chamber diameter suggestive of dilated cardiomyopathy. To test if gene therapy could mitigate the cardiac aspects of PA, different adeno-associated virus (AAV) vectors expressing the PCCA transgene were used to treat A138T mice. Liver-targeted AAV8 treatment reduced systemic metabolites in the blood well, but it mediated only slight correction of the cardiac disease. In contrast, muscle-targeted AAV1 therapy reduced cardiac hypertrophy and corrected cardiac remodeling. These results show that while liver-directed therapy which would be analogous to a liver transplant provides systemic benefits, it does little to correct cell defects that occur within in the heart. In contrast, muscle-targeted therapy blunts systemic metabolites while also better treating cardiac manifestations of the disease. These results are the basis for a pending proposal to translate the muscle-targeted AAV gene therapy vector towards clinical testing.

**Immunological Perturbations in A138T PA Mice.** Infections can precipitate dangerous metabolic events in patients with PA. There are also concerns about whether routine vaccination might precipitate similar consequences in patients. We have recently probed the immune systems in A138T mice to determine if they show perturbations in this system.

We tested whether the mice could repel infection by adenovirus, one of the viruses that causes the common cold. We found that A138T mice were infected at much higher levels than normal mice. When these mice were followed, they mounted a normal antibody response to the viral challenge. This suggested that the animals may have problems with innate immune responses that occur soon after infection, but that their adaptive immune response that protects against later infections was intact.

When we analyzed the blood of A138T mice, they had only slight reductions in red blood cells, white blood cells, platelets, and antibodies. This would be consistent with the mice having normal adaptive immunity. (cont. pg 3)

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.

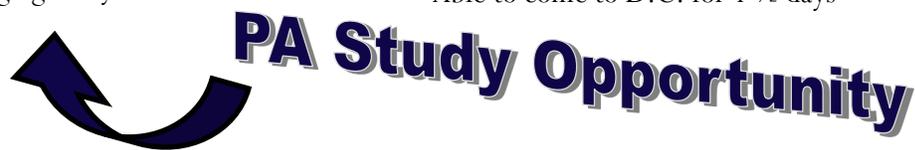
## MRI STUDY TO LOOK AT THE EFFECTS OF PA ON BRAIN

Dr. Andrea Gropman and colleagues at the Children's National Medical Center and Georgetown University Center for Functional and Molecular Imaging are conducting a study to look at the impact of Propionic Acidemia on brain biochemistry and function. The study involves neurocognitive testing and a 2 hour MRI study without sedation.

Travel is reimbursed and there is a stipend for participation. If interested, please contact Nicole Ulrich at 202-476-6034 or [nulrick@childrensnational.org](mailto:nulrick@childrensnational.org) and mention "Dr. Gropman's imaging study for PA".

In order to be eligible, the following criteria must be met:

- Diagnoses of PA
- Age 6-40 years
- Good health, stable, not in metabolic crisis
- Able to lie on a table for up to 20 minutes at a time
- Able to have a scan without sedation
- Not claustrophobic
- Able to be scanned safely, i.e. no metal in body
- Able to come to D.C. for 1 ½ days



## BARRY LAB (CONTINUED FROM PG. 2)

While these parameters were largely normal, the largest effect was a 50% reduction in granulocytes. This would be consistent with a diagnosis of granulocytopenia in humans. Granulocytes are interestingly part of the innate immune system and are involved in repelling viral, bacterial, and fungal infections. Humans with certain types of granulocytopenia can have recurrent ear and sinus infections, pneumonia or bronchitis, and other problems. These data suggest that A138T PA mice may manifest some aspects of immune system perturbations seen in patients.

**Neurological Symptoms in A138T PA Mice.** The A138T mice have some symptoms that mimic neurological effects in PA patients. For example, A138T mice have 4-fold elevations in methylcitrate and elevations in lactate or glutamine/glutamate in their brains. Some mice also exhibit behaviors associated with seizures, but this does not occur in all of the animals.

Assessing neurologic phenotypes in mice is more complex than in humans, since they cannot speak nor

perform neurological tests. One way to probe this is to perform neurobehavioral tests wherein the mice perform certain tasks like crossing a rotating cylinder or exploring a new space or remembering how to find their way in a maze.

We have recently performed selected neurobehavioral tests in the A138T mice. When they are allowed to explore a new space, they exhibit behaviors consistent with a heightened level of anxiety. When they perform "novel object recognition" tests, they tend to shy away from new objects. Mice seek out new objects in the search for food, so this behavior is again suggestive of elevated anxiety. They also show a lack of discrimination for the presence of a novel object in a familiar environment which suggests some level of cognitive defect.

We are in the midst of testing a larger batch of mice by this test and intend to treat them by gene therapy to see if we can attenuate any of the observed neurological phenotypes.

*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](mailto: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.*

## CINDY'S STORY

Hi, everybody. My name is Tad. Firstly I should say I am fortunate. I am fortunate to get the opportunity to join the university, where I met my girlfriend, who became my wife 10 years later. I am fortunate to get my present job as a petroleum geologist after I got my PHD degree from RIPED, where I met a lot of good friends. I am fortunate to have a beautiful daughter, Cindy, in 2012. However, things changed from the day I received a call, which told me the results of my daughter's lab test. The doctors suspected my 20-day old daughter to have PA. Looking at the cute baby, we all doubted the results. But we went to a doctor the next day, and did some normal lab tests. According to the tests result, the doctor didn't think Cindy has PA. Then we went back home, with a burden unloaded.

But after that day, my wife got nightmares nearly every night. I have to say, I began to believe the saying of mother-daughter-one-heart. After one week, we decided to do some more professional tests to confirm the situation. About one months later, all the results reflected that Cindy does have PA, which is PCCB in subtype. The result shocked us, and even the doctor. She said she never see a PA baby in such a good condition during her career. Then we began to give her special diet with XMTVI Analog formula and SigmaTau L-carnitine. In the beginning we know little about PA, so we cut off every milk including her mother's milk. What a pity baby and stupid parent!

I want to say I am fortunate again, thanks the God. We then met a professional doctor who told us how to feed Cindy. Before that we suffered a lot, even Cindy had to be sent to PICU once when she was 1 year old. After that, Cindy began to sit, walk, talk at normal age. But

then, things became worse, the XMTVI Analog was forbidden to sale on Mainland China. We have to change into another formula, OA1, which is difficult to buy in China. During the period, I joined in to an PA organization in China. We talked a lot there and learned a lot from each other. There are totally about 134 parents with PA or MMAW kids. The organization is really awesome! And as you all know, as most of PA kid, now Cindy begins to dislike the formula and her food, she wants to eat meat. She is now still in the hospital for the past 20 days eating less. So I want to change her diet according to my self's knowledge, for we cannot get more suggestions from our doctors any more. I will add more formula with little protein but high energy and other minerals.



Now I am in the USA to do a co-research program leaving my family in China. One of the reasons why I choose to

come here from such a long way and in such a critical time for my family is that I want to learn something about PA here in the USA.

Thanks the God. I met many good people here, and joined the PAF, which gives me a lot of help. This including feeding methods, formula information, medicine et al. Even I have read a good news of breaking through in the cure of similar kinds of disorder from the newsletter. The stories on the newsletter encouraged me a lot. I have told and will continue to bring all I have learned from here back to the patients in China. And now I am collecting the gene testing results of kids with PA in China. I hope one day this results can be helpful for the people who are doing researches on PA.

## GABRIEL'S STORY

As is often the case with so many children who are born with an organic acidemia, Gabriel's first year of life was full of difficulties and hospital stays. After his initial crisis at 24 hours of age, Gabriel had lots of episodes of metabolic decompensation, and high ammonia levels, compounded by undiagnosed epilepsy (infantile spasms). Nevertheless, he started to stabilize around the time of his first birthday, and you can check out a summary of Gabriel's first five years of life in a previous report we wrote for PAF.

During his first year of life, Gabriel spent 9 months with a nasogastric tube, which was so uncomfortable that it greatly contributed to his decision to stopping eating. But he got a G-tube at 15 months of age, and quality of life improved, not only for him, but also for the rest of the family. Through the G-tube, we started managing him much better at home because we did not have to rush him to the hospital every time he started throwing up. He became even more stable at the age of 3, and he started preschool also then. At that time, Gabriel didn't have words and was incredibly delayed in all domains (especially motor and language) but he has overcome a lot and has been steadily progressing ever since. This was a little miracle to him thanks to an amazing teacher. Indeed, one very important thing for us is that Gabriel has not stopped developing, even though he makes progress at this own pace (meaning, very slow!).

At the age of 5 we found a school that could target much better his language delays and lack of socialization skills. He spent 5 incredible years at this fantastic setting. It was a great program for him. Although still very delayed, Gabriel now chats a lot and understands and speaks both English and Spanish (both his father and mother are native Spanish speakers) although he is clearly dominant in English. He now has a few friends at school and shows more interest for group activities, like soccer. He is no longer afraid of noise at the movies and initiates conversations with other children in the park. Academically, Gabriel is quite delayed but the fact that he is reading and writing is a miracle to us. He is also

able to do very simple math.

The other little miracle we experienced with Gabriel is that at the age of 6 we found a wonderful feeding therapist (who was actually a special-ed teacher with experience in feeding issues from the behavioral point of view). She taught Gabriel how to eat (after 6 years of being 100% tube-fed). It was a very slow process but Gabriel now eats like 50% of his nutrition by mouth with a very wide variety of (very healthy!) foods: rice, pasta, vegetables, fruits and so on, everything with low protein, although he also eats the occasional egg or fish sticks. The reason why he only eats like 50% by mouth is because he still has very poor oral motor skills, and is very slow chewing and swallowing. Regardless, the fact that Gabriel can eat by mouth has helped tremendously to normalize our family: we go more often to restaurants, and Gabriel is happy to seat at the table with us and even request his own food from the menu. He has gained so much confidence as a result of eating by mouth!



In practical terms, the biggest challenge that Gabriel faces right now is his executive function (he has very poor coordination and motor skills, although he can run relatively well) and his language (he is diagnosed with a language disorder and although his IQ is a bit low, the psychologists think that part of the problem is his severe language issues). As a result of this, Gabriel attends a special-education school with highly individualized education. His class has two teachers and seven other children, and Gabriel still receives a lot of therapy at school (OT, PT, ST).

What is crucial about Gabriel's life is that he is a very happy child. He loves water and has been learning how to swim for two years now and is able to execute quite a nice stroke (although the coordination with breathing is very difficult for him). In the past two winters he has also been trying adaptive ski and has absolutely embraced it. He has been traveling quite extensively around the world since he was 2 months old (we go often to Mexico and Spain to visit our families, and he loves playing with his cousin Marifer). Last year, the Make-a-Wish Foundation granted Gabriel a trip to Japan. He wanted to visit Tokyo, the city where Lightning McQueen (from the movie "Cars 2") races (cont. pg. 6)

## PAF EVENT & FUNDRAISING SPOTLIGHT

### PAST EVENTS & CAMPAIGNS:

- McKinley Bracket Challenge: \$435
- Ohio Families 10th Annual Corn Hole Tournament  
September 26th, \$10,000+
- Several Ohio runners were on TEAM GWEN at the Nationwide Children's Hospital Columbus ½ & Full Marathon on Sunday, October 18th. Gwen was a Children's Miracle Mile Patient Champion for Mile 8 representing metabolics at the race! (photo right)

### ONGOING ONLINE TOTALS (as of 10-20-2015)

Igive: \$4183  
Goodsearch: \$1410  
AmazonSmile: \$86

**Corporate Matching Gifts for cash donations or volunteer time may enable you to double your donation. Check with your HR department to see if they match. It makes a big difference!**

### DEDICATED GIFTS FROM INDIVIDUALS:

Among the many contributions received, the following is a list of some that were dedicated to those who have inspired the giver.

- **In Honor Of:** Kate Lowry, Gwen Mouat, Jordan Franks, Kristin Boecker, Reuben Kleckley, Brett Young
- **In Memory Of:** Christopher Moreland Jr., Vincent Philip Franze, Nicholas Alexander Phillips, Angelica Stageman, Connor McKillop



## GABRIEL'S STORY (CONTINUED FROM PG. 5)

in the middle of the night lights. It was an absolutely amazing experience and a very beautiful memory that hopefully will last forever in all of us!

For the past year and a half, Gabriel has been learning how to cook with a special-ed teacher. Although Gabriel is not very big eater he enjoys cooking very much, and we decided to develop a program whereby he could learn new skills and gain independence at the same time. So, every Saturday he prepares a shopping list for a new recipe, goes to the supermarket, chooses the ingredients and pays. Ideally, we are aiming for him to do all this independently at some point. When he gets home, he starts smelling, chopping and stirring. He is now able to turn the gas knobs on, boil water and add salt and pepper to a simple dish! He really, really enjoys cooking, and this is the one thing that takes him away from his video games and such. His new addition to the menu has been "pumpkin pie cheese cake". He just cannot have enough of it! But he cooks all kinds of dishes from a Thai salad to Mexican corn soup. Although he often does



Gabriel and brother, Alex

not like the new dishes he makes, he always, always tries them. This plan has been really working very well to the point that Gabriel has expanded the repertoire of foods and flavors he eats now, he is no longer afraid of trying new foods away from home, and he is slowly gaining some skills that, we feel, will be valuable in the near future.

Looking forward, we think Gabriel's life will be very challenging, as he is unlikely to be able to live independent-

ly. However, we feel blessed that he is such a kind and caring child who tries to enjoy new adventures, no matter the challenge. So, we try not to think too hard about what it will be, but focus instead on who Gabriel is and what he does right now, taking one day at a time!

Please, feel free to contact us if you would like to learn more details about Gabriel's management or activities.

Cheers, Marisa Cotrina and Juan Carlos López  
mlcotrina@gmail.com

# ANNUAL REPORT

## FINANCIAL REPORT

### Revenue:

Contributions: \$56,427  
 Interest Income: \$119  
 In Kind Donations: \$1,180

**Total Revenue:** \$57,726

### Expenses:

Research Grants: \$57,732  
 Programs & Outreach: \$735  
 Printing (in-kind): \$1,180  
 Fundraising: \$162  
 Management & General Expenses: \$977

**Total Expenses:** \$60,786

Cash Assets 8/1/2014: \$145,413

Cash Assets 7/31/2015: \$142,353

## PROGRAM ACCOMPLISHMENTS

### Research: Grant Disbursement:

- \$39,572 Michael A. Barry, Ph.D, Mayo Clinic College of Medicine, "Neurologic Phenotypes and Therapy in Propionic Acidemia Mice."
- \$18,159 Loren Pena, M.D., PhD., Duke University, Durham, NC, "A prospective study of biochemical parameters reflective of metabolic control in propionic acidemia"

**Outreach:** Distributed fall and spring newsletters to affected families, clinicians, and donors

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Donations made by board members totaled \$1,200.



**Thank you for all donations and the kind notes we receive throughout the year. Your support overwhelms us and continues to be a source of inspiration. PAF couldn't do what we do without your incredible support.**

***We want to hear from you! Have a PA story to tell, event to promote or news? Spring newsletter submissions due by February 1, 2016!***

## Help Us Find the Cure!

Name \_\_\_\_\_

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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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