SEARCHING FOR A CURE HOPE FOR OUR CHILDREN

# Propionic Acidemia Foundation

VOLUME 1, ISSUE 25 FALL 2018

## PAF Warrior Wisdom Conference

**October 19-21, 2018**
**Nationwide Hotel & Conference Center**
**100 Green Meadows Drive South, Lewis Center, OH 43035**

**Friday, October 19th**

6:30pm-8:30pm Registration, Reception with light snacks, New Parent Orientation

**Saturday, October 20th**

8:00am-8:30am Registration

8:30am-5:00pm Conference– Presentations, Family Panel, and Visit Exhibitors.
Topics Include: Propionic Acidemia, Secondary Complications, Nutrition Management and Guidelines, Nutrition during Menstruation and Pregnancy, PAF Updates (detailed agenda to be posted on website)

5:00pm-9:00pm Dinner, Social & Networking Time

**Sunday, October 21st**

Run for PAF or cheer on participants in the Nationwide Children's Hospital Columbus Marathon/Half Marathon! (Separate Registration) Location and directions for cheering on our PAF Runners available at the conference.

**HOTEL INFORMATION**

Special Group Rate: $119.00 plus taxes, includes breakfast.

Please call or email Kelsey McClincy at (614) 602-0114 or kelsey.mcclincy@onelodging.com Monday through Friday from 7:30 am- 4:00 pm to make your reservation. Reserve your room before they sell out or by September 20th whichever comes first.

***PLEASE JOIN US IN OCTOBER!***

***REGISTER ON-LINE OR CALL 877-720-2192 FOR MORE INFORMATION.***

**PA Registry**

Help move research forward for propionic acidemia. Participate in the Propionic Acidemia International Registry. As of September 1st, there are 64 participants. For more information on joining the registry, or to update your information, go to www.paregistry.org.

## 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.

# PAF AWARDS GRANT TO NIH

**PAF Awards a $32,912 Grant to Oleg Shchelochkov, MD and Charles P. Venditti, MD, PHD**
**National Human Genome Research Institute, National Institutes of Health**

"Diversion of Isoleucine and Valine Oxidative Pathway to Reduce the Propionogenic Load in Propionic Acidemia."

Patients with propionic acidemia require lifelong protein restriction. In addition to taking a protein restricted diet, many propionic acidemia patients are also prescribed medical formulas. This dietary approach aims to decrease the intake of four amino acids that can become propionic acid. These four amino acids - isoleucine, valine, threonine, and methionine - are called essential, because they cannot be made in the human body and need to be supplied from foods. Too much protein intake creates a situation where excess can lead to a buildup of propionic acid in the body. On the other hand, limiting these four amino acids too much can lead to poor growth. Therefore, patients' diets are optimized to minimize propionic acid production while encouraging good growth. We wonder whether it is possible to increase dietary protein intake while minimizing the risk of propionic acid buildup.

To answer this question, we are planning to do a series of experiments in zebrafish. Why use zebrafish? Zebrafish share significant similarity to humans in how they process propionic acid. In addition, zebrafish reproduce and mature quickly, which are very important qualities to help search for new drugs that could be used to treat propionic acidemia. Our zebrafish are kept in a special building where the animals are being cared for by a dedicated team that includes scientists, veterinarians, engineers, aquatic specialists, and many others. They check on fish and feed them several times a day, maintain fish tanks, and keep their water very clean.

This type of facility is unique and had enabled our studies of metabolic diseases in zebrafish. Our ongoing studies have shown that zebrafish affected by metabolic diseases have symptoms that are very similar to patients. Even with treatment, affected fish have difficulty growing, get tired easily, have poor appetites and sometimes perish before adulthood. Using special genomic tools, we are planning to change in how the fish processes protein to direct it away from becoming propionic acid. As we make these changes to the biochemical pathways of propionic acidemia zebrafish, we will be carefully watching how these treatments improve their growth, development, appetite and survival. These experiments will help us understand how we can potentially reduce propionic acid toxicity while helping patients achieve a less restrictive diet.

# NOVEL THERAPIES FOR PROPIONIC ACIDEMIA

**Nicola Brunetti-Pierri, MD,**
**Fondazione Telethon, Italy**

This proposal was focused on the characterization of a fish model of propionic acidemia (PA) and on the development of novel therapies. The PA medaka fish model was found to recapitulate several clinical and biochemical features of the human disease, including reduced survival and locomotor activity, hepatic lipid accumulation, increased propionylcarnitine, methylcitrate, and propionate. Moreover, PA fishes showed better survival when fed with low-protein diet.

To gain insight into the disease pathogenesis and to search for potentially novel therapeutic targets, we performed an unbiased 3'-mRNA-Seq and NMR-based metabolome analyses. Both analyses showed global differences between PA and wild-type (wt) medaka. Interestingly, metabolism of glycine and serine resulted affected both at transcriptional and metabolites level and further studies are ongoing to investigate the role of these changes in the disease pathogenesis. Moreover, we found a marked increase in protein propionylation in PA fishes compared to wt controls. Protein propionylation is a post-translational modification occurring under normal (Continued next page)

# TARGETING SERINE AND THIOL METABOLISM IN PA

**Hilary Vernon, MD PhD, Johns Hopkins University**

While it has been known for several decades that dysfunction of the enzyme propionyl-CoA carboxylase underlies propionic acidemia (PA), many key downstream metabolic adaptions to this primary defect are not well defined. In our research, we developed and studied a new cellular model of PA, with the goals of understanding how the cell is affected in PA, and to identify new pathways for potential treatment targeting.

We initially studied both protein expression in fibroblasts (skin cells) from individuals with PA, and metabolites in urine from individuals with PA, and discovered changes in pathways related to serine metabolism. Serine is an important amino acid that is involved in the synthesis of folate intermediates, glutathione, and other important cellular metabolites. Serine metabolism is of particular interest because it has also been shown recently to be dysregulated in other mitochondrial diseases, and there is a growing interest in how to target this pathway for therapeutic intervention.

In order to more closely study these findings, we developed a new cellular model of propionyl-CoA carboxylase deficiency, where we used CRISPR technology to mutate the PCCA gene in a kidney cell line called HEK293. This new model cell line has important biochemical hallmarks of PA, including absence of the PCCA protein, elevated propionyl-carnitine, very low methylmalonyl-carnitine, and elevated glycine. We discovered that when these cells are in the growth phase, they express genes involved in serine synthesis at higher levels than cells that have normal propionyl-CoA carboxylase activity. We further discovered that the PA cells are very sensitive to deprivation of serine in their culture media, and grow slower than cells with intact propionyl-CoA carboxylase activity. This growth abnormality is not seen when the cells are grown in media that contains serine. Interestingly, we looked at these same pathways in a CRISPR model of methylmalonic acidemia, a closely related disorder to PA, and while we found some overlap in sensitivity to serine, the gene expression patterns we different. This highlights the biochemical uniqueness of PA. Currently, we are completing flux metabolomics studies in these cells, which will determine exactly what this serine is being metabolized to, and we expect these experiments to be completed by the end of August. In our next steps, we plan to study how treating the cells with different metabolites may alleviate this serine growth defect.

We would like to sincerely thank the Propionic Acidemia Foundation for supporting our research. The funding we received has led to important breakthroughs in our work, and we are excited to continue to move this research forward in the coming years.

# NOVEL THERAPIES... (CONTINUED FROM PAGE 2)

conditions but its physiological role is unknown. Like protein acetylation, it is likely involved in regulation of gene expression, protein-protein interactions, and enzyme function. Interestingly, NAD-dependent sirtuins that are responsible of deacetylation of multiple proteins and have also de-propionylating activity, were significantly reduced in PA fishes. We speculated that aberrant protein propionylation in PA is toxic and proteomic studies are ongoing to reveal proteins with aberrant propionylation. With the support of this grant several drug candidates have been also investigated with the goal of developing new pharmacological approaches for PA.

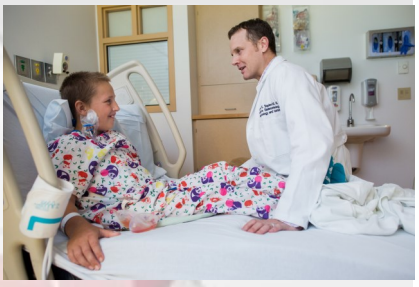
In conclusion, we performed extensive phenotyping of the PA fish model that can be useful to unravel novel disease mechanisms and therapeutic targets.

# LIVER TRANSPLANTATION FOR PROPIONIC ACIDEMIA

**Part 2: Outcomes Following Liver Transplantation in Children with PA and MMA**

**James Squires, MD, MS**, Dr. Squires is a liver disease specialist at UPMC Children's Hospital of Pittsburgh and an assistant professor of pediatrics at the University of Pittsburgh School of Medicine.

**Jodie M. Vento, MGC, LCGC**, Jodie Vento is a genetic counselor and manager of the Center for Rare Disease Therapy at UPMC Children's Hospital of Pittsburgh.



*Part 1 of this article, published in the Spring 2018 issue, provided answers to questions that families may have about what to expect from a liver transplant for a child with Propionic Acidemia (PA). Here, in Part 2, the authors summarize and explain the findings of a recent study of outcomes in children with PA and methylmalonic acidemia (MMA) who received liver transplants at UPMC Children's Hospital of Pittsburgh.*

***Why did you do this study?***

Before we get to why we did this study, please allow us to back up a bit and briefly discuss the history of liver transplantation for PA and MMA, which was first proposed in the early 1990s. Because the enzyme deficiencies that cause PA and MMA exist throughout the body, not just in the liver, liver transplantation was never expected to be a cure for these diseases. The thinking was that by providing enough functional enzyme to minimize, if not eliminate, metabolic crises-—the most severe complications of PA and MMA for affected children, as well as one of the most frightening features of these diseases for families—a liver transplant could enhance stability and improve quality of life for affected children.

In recent years, policies on the allocation of donor livers in the United States have changed to give priority to patients with PA and MMA because of their risk of sudden, life-threatening metabolic crises. As a result, children with these disorders can now be listed for a liver transplant based on their diagnosis alone rather than on disease complications or severity.

A recent study, based on statistical analysis, found that liver transplantation for PA and MMA may increase both the length and quality of patients' lives and decrease health care costs over a patient's lifetime. However, because PA and MMA are rare disorders, it has been difficult to gather a strong body of evidence showing how well patients fare after undergoing a liver transplant.

The Pediatric Liver Transplant Program at UPMC Children's Hospital of Pittsburgh was established in 1981 by world-renowned transplant surgeon Thomas E. Starzl, MD, PhD. Our Director of Pediatric Transplantation, George Mazariegos, MD, FACS, pioneered liver transplantation for children with metabolic diseases in 2004. Since then, UPMC Children's has performed more than 330 liver transplants for children with metabolic diseases, more than any other transplant center. We've also performed more liver transplants in children than any other center in the United States and more living-donor transplants than any other pediatric center in the country. Our one-year survival rate for pediatric liver transplant patients is 98%, exceeding the national average of 95%, according to the Scientific Registry of Transplant Recipients (January 2018 release).

We decided to do this study because, given the breadth and depth of our experience in this field, we thought that we could make a useful contribution to medical knowledge by gathering and evaluating all of the information available to us on outcomes for all of the patients who have undergone a liver transplant for PA or MMA at our institution.

***How did you do this study?***

We searched our medical records database to identify all patients with a diagnosis of either PA or MMA who received either a liver transplant or a combined liver and kidney transplant between 2006 and 2017.To comply with patient privacy regulations, we first removed any and all information that could personally identify these patients. Then we examined data from their medical records and recorded information such as their age and family history, medical treatment received prior to the liver transplant, laboratory tests performed, and how they fared both immediately after the transplant and in the following months and years.

***What did the study find?***

We identified a total of nine patients with PA (three patients) or MMA (6 patients) who had undergone a liver or liver and kidney transplant at UPMC Children's between 2006 and 2017. The age at which patients received their transplant ranged from one year old to 21 years old; the median, or midpoint, was nine years old. Five patients were female and four male. Eight of the nine patients had been diagnosed during their first week of life; one patient was diagnosed at age eight months.

Prior to the transplant, all of the patients had been treated with protein restriction and carnitine supplementation. Several were also receiving medication to reduce ammonia levels in the blood. Eight of the nine patients were being fed by a gastrostomy tube (also known as a "G-tube"). All were experiencing frequent metabolic crises that often required hospitalization. (Continued next page)

# Liver Transplantation (continued)

Additional disease-related complications included cardiomyopathy (damaged heart muscle), metabolic stroke, pancreatitis, and low blood cell counts.

Five of the six patients with MMA received combined liver and kidney transplants. One patient with MMA and all three patients with PA underwent liver transplants only. Patients' median post-transplant length of stay in intensive care was just short of 30 days, while the total transplant-related hospital stay averaged 55 days. Patients were followed after their transplant for a median of 3.5 years (range one year to more than 11 years).

Six of the nine patients developed symptoms of liver rejection; one patient developed symptoms of kidney rejection. Rejection episodes were treated with steroids and higher doses of anti-rejection medication to suppress the immune system. None of the nine patients experienced transplant failure.

Two patients needed treatment for blood clots in the main artery that carries blood to the liver. A third patient needed treatment for a blockage in a vein that transports blood from the liver back to the heart.

Four patients experienced a build-up of bile in the liver that was caused by a blocked bile duct and required treatment with a biliary catheter. At the last follow-up, three of the four patients had been able to discontinue use of the biliary catheter.

Five patients developed viral infections that required treatment. No patients experienced a complication known as post-transplant lymphoproliferative disorder, a dangerous rapid increase in white blood cells that can sometimes occur in people who are taking medication to prevent rejection of a transplanted organ.

No patients have experienced metabolic crises since the transplant. All nine patients showed improved metabolic control—indicated by normal levels of lactic acid in the blood—during the first month after the transplant. Kidney function stabilized or improved in all patients with MMA. At the two-year post-transplant assessment, heart function had improved in a patient with PA and severe cardiomyopathy.

***What conclusions can be drawn from the study's findings?***

In this study of nine children with PA or MMA who were followed for an average of 3.5 years, we show 100 percent survival for both patients and their transplanted organs.

For MMA, these findings are similar to those of other recently published reports. For PA, although our population is relatively small (three patients), our finding of 100 percent survival for both patients and transplanted organs stands in contrast to other published reports that found poor survival among patients with PA following a liver transplant.

Still, many patients experienced complications in the period immediately before, during, and after the transplant. The high rate of complications underscores the complexity of these metabolic diseases. The most common complications were those involving the blood vessels, including blood clotting in the main artery of the liver. This complication has been previously reported.

All patients had reduced levels of lactic acid in the blood, indicating improved metabolic control, both shortly after the transplant and at later postoperative follow-up. Complications such as kidney disease (in patients with MMA) and cardiomyopathy (in patients with PA) stabilized and improved after transplantation.

The fact that no patients experienced metabolic crises after transplantation indicates that partial enzyme replacement via a liver transplant enabled a "resetting" of patients' metabolic fitness.

At UPMC Children's our approach to nutritional support after a liver transplant has been to gradually ease protein restriction, with the goal of establishing a long-term individualized level of support for each patient. It is unlikely that protein restriction can ever be completely eliminated. However, the results of this study show that—with close monitoring by an experienced interdisciplinary team—protein restriction can safely be relaxed, in an individualized fashion, after a liver transplant.

***What do the study results mean for children with PA and their families?***

A liver transplant cannot cure PA. It can, however, reduce or eliminate metabolic crises and result in greater stability and better quality of life for children with PA. The decision as to whether a liver transplant is right for your child with PA is one that every family must make for themselves, based on their knowledge of their child and in consultation with a multidisciplinary team of experts who specialize in liver transplantation for metabolic diseases.

This study adds to the increasing body of evidence that liver transplantation can be performed safely and successfully in patients with severe, complex metabolic conditions such as PA and MMA, especially when performed at centers with broad and deep experience in the management of these highly challenging conditions.

*Reference: Critelli K, McKiernan P, Vockley J, Mazariegos G, Squires RH, Soltys K, Squires JE. Liver Transplantation for Propionic Acidemia and Methylmalonic Acidemia: Peri-operative Management and Clinical Outcomes. In press, Liver Transplantation. Accepted for publication June 2018.*

# PAF EVENT & FUNDRAISING SPOTLIGHT

**UPCOMING/ONGOING EVENTS**

- **Sep 29- 13th Annual Tailgate Party & Corn Hole Tourney for PAF**, Gahanna, Ohio, 4:00 p.m. at the Goat in Gahanna. For more information go to gwenforacure.com
- **Oct 19-21- Warrior Wisdom Conference,** Lewis Center, Ohio
- **Oct 21- Team PA Runners, Nationwide Children's Hospital Columbus Marathon**
- **Pups for Propionic Acidemia 2019 Calendar-** Available for sale at fall events! If interested in purchasing one, contact Michelle Ellis at im2alesmom@yahoo.com.

**CORPORATE MATCHING GIFTS AND VOLUNTEER HOURS DONATIONS:**

- **Corporate Matching Gifts:** This may enable you to double your donation. Check with Human Resources to see if your employer matches. It makes a big difference.
- **Volunteer Hours**: Some companies have a volunteers program and will donate based on your volunteer hours. PAF is always looking for volunteers. Please check with Human Resources to see if they have a program.

**MAKE YOUR ONLINE SHOPPING COUNT WITH:**
AmazonSmile, Igive, and Goodsearch

**FACEBOOK:** Thank you to all of our Facebook Fundraisers: Patt, Amber, Carrie, Laurel, Amy, Cindy and Jessica. Thank you for making a difference!

**DEDICATED GIFTS FROM INDIVIDUALS:**
Among the many contributions received, the following are some that were dedicated to those who have inspired the giver.

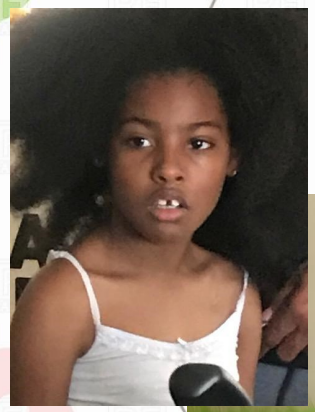
**In Honor Of:** Reuben Kleckley's Birthday, David Huffman's Birthday, Trent McKinley, Gabrielle Millett, Kate Lowry, Gabriel Lopez, Grant and Sebastian Moss

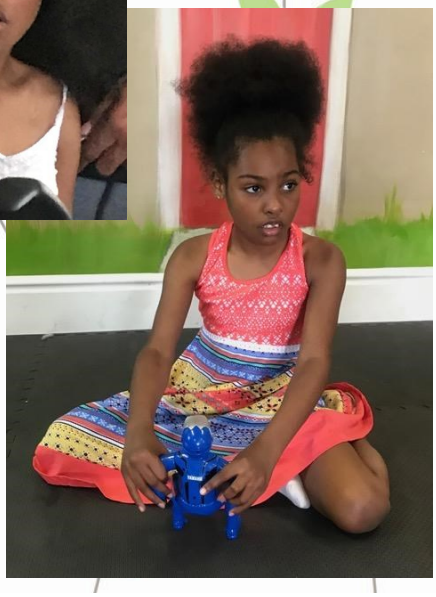
**In Memory Of:** Kirstyn Tripp, Connor McKillop, Jordan Franks, Cadybug

Join the PA Runners team with a distance and race of your choice. All abilities welcome! Contact Marisa Cotrina for more information, teamPAR4@gmail.com


# GRACE-MARIE'S STORY

Grace-Marie was born on November 14, 2007 a day before her dad's birthday. She was born at 7:30 a.m. 5 lbs. 2 oz. I was so happy to finally see her for the first time. That's when it first started. Grace's heart beat was going really fast so they wanted to check her out really good before I could hold her. The morning turned to night and I still could not see Grace. Grace would not eat so they wanted to watch her in the NIC (Neonatal Intensive Care) over night. One day turned into seven in the NIC. Grace began to eat a little but was not very responsive to touch. She also began to not keep any milk down therefore she was becoming very lethargic. Day by day Grace was slipping away. She was transferred to UCLA where she could be cared for better. It was at UCLA that her New Born Screening revealed she had Propionic Acidemia.





The doctors explained to us that it is a rare metabolic disorder.

For the first two and half years of Grace's life was full of doctor appointments and emergency room visits. Some that left me pretty devastated, Grace received a permanent port so that she could have blood draws and kept it for the next six years. It was magical and helped out a lot whenever she was unstable, she also had a G-Tube placed so she can receive her special diet to help her remain stable and receive all of the nutrients she needs to grow. Grace is ten now, almost eleven, and we continue to take it day by day, some good and some not so. Grace continues to have physical, speech, occupational and behavioral therapy throughout the week, which keeps us busy along with a full day of school. What I have learned the most so far from this experience is to be as present as I can, that way I can learn as much as I can on this journey one day at a time.

Grace is one of the great joys in our life.

# ANNUAL REPORT FY 2017-2018

## FINANCIAL REPORT

**Revenue:**

| | |
|---|---|
| Contributions | $57,776 |
| Interest Income | $4,789 |
| **Total Revenue** | $62,565 |

**Expenses:**

| | |
|---|---|
| Program service | $56,684 |
| Management & General | $1,967 |
| Fundraising | $585 |
| **Total Expenses** | $59,236 |
| Cash Assets 8/01/2017 | $380,221 |
| Cash Assets 7/31/2018 | $383,550 |

**Board Disclosure:**

Donations made by board members totaled $643.

## PROGRAM ACCOMPLISHMENTS

- Awarded research grant to Oleg Shchelochkov, M.D. and Charles P. Venditti MD, PhD at National Institutes of Health for "Diversion of Isoleucine and Valine Oxidative Pathway to Reduce the Propionogenic Load in Propionic Acidemia."
- 63 Participants in PA Patient Registry
- Distributed fall and spring newsletters to affected families, clinicians, and donors
- Attended and exhibited at Genetic Metabolic Dietitians International meeting- Orlando, FL
- Attended and exhibited at Society for Inherited Metabolic Disorders meeting- San Diego, CA
- Participated in "Partners in Progress: Parents and Scientists Catalyze Research in Rare Disease"- Houston, TX

## WARRIORS BIRTHDAY CLUB

**The students at Oak Lawn-Hometown Middle School made such amazing and memorable cards last year for participating families. We are thankful they have volunteered to do it again this school year. Sign up at: http://www.pafoundation.com/warriors-birthday-club/**

**If you signed up last year, you will need to sign up again so we have current information.**


***Help Us Find the Cure!***

*Name*_____ *Please send an acknowledgement to:*

*Address*_____ *Name*_____

*City, State, Zip* _____ *Address*_____

*Phone*_____ *City, State, Zip*_____

*E-mail*_____

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

- *By providing your e-mail address you are opting in to receiving e-mails from the Propionic Acidemia Foundation. We will not share your information with those outside of the foundation.*
- *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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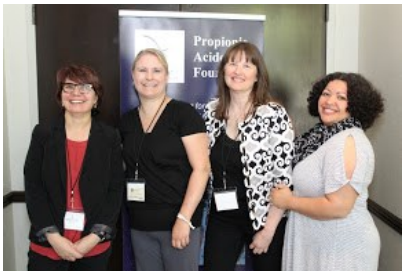
# Propionic Acidemia Foundation





Join and follow Propionic Acidemia Foundation on Facebook

**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 March 1, 2019!***

*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.*