SEARCHING FOR A CURE HOPE FOR OUR CHILDREN

Propionic Acidemia Foundation

VOLUME 1, ISSUE 31 FALL 2021

Pounding the Pavement for PAF

In 2002, I decided to run my 1st marathon. After watching thousands of people run past my apartment in German Village in Columbus, I wanted to give it a try and check it off the bucket list. Well, I got hooked and have now run 26 marathons! In 2015, I was lucky enough to run the Columbus marathon to support Gwen Mouat, who was named a patient champion for the race. I've known Gwen since the day she was born as her parents, Tom and Jen, lived right next door. Over the last 16 years, with immense love and caring from family and friends, I have watched Gwen battle PA with resilience and resolve. To see her thrive and succeed has been such a joy. On November 7th, I'm running the 50th NYC marathon to raise funds for PAF. This foundation does such incredible work to raise awareness and support research towards finding treatments for PA and hopefully a cure. Raising money for such a worthwhile cause to help those afflicted with PA has been incredibly rewarding for me. For the last 15 years, I've enjoyed participating in the Mouat's annual cornhole fundraiser. Now, I'm ready to pound the pavement and contribute in a different way.

WE'VE MOVED!

Our new mailing address:

Propionic Acidemia Foundation
PO Box 151
Deerfield, IL 60015-4421

PA Registry

Help move research forward for propionic acidemia. Participate in the Propionic Acidemia International Registry.

As of October 15, there are 115 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.

ANNUAL REPORT 2020-2021

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.

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2020-2021 Financials

Revenue:	
Contributions	$139,492
Interest	$650
Total Income	$140,142
Expenses:	
Program services	$174,565
Management & General	$1,978
Fundraising	$221
Total Expenses	$176,764
Cash Assets 8/01/2020	$468,376
Cash Assets 7/31/2021	$431,754

Board of Directors

Jill Chertow, President
Brittany Smith, Treasurer
Angela Waits, Secretary
Maria L. Cotrina

Letter from the Board of Directors

We are happy to share with you our annual report.

This past year has been one like no other; having to handle the day-to-day life with Propionic Acidemia can be very difficult, but add in a pandemic and it has stretched families and their providers.

As an organization, we have had to make adjustments. PAF granted research grant extensions to our grant recipients as labs were closed. We had to postpone an in-person conference we were planning, but were able to hold a virtual conference in October 2020 with international participation.

We hosted virtual events, including dance parties and art classes over the past year. We also hosted a PA chat for families to share their experiences. Collaborative meetings with other rare disease groups over Zoom provided information on low protein diets, advocacy, and clinical trials.

We thank you for your support.

Board Disclosure: Donations made by board members totaled $600.

PROGRAM ACCOMPLISHMENTS

Grants Awarded

- Awarded $49,953 grant to Pawel Swietach, DPHIL, at the University of Oxford, England as a new grant for the project entitled: "Aberrant protein propionylation and distinct histone marks in propionic acidemia: new disease mechanisms and risk factors for cardiac disease."
- Awarded $50,000 grant to Sander Houten, Ph.D. & Robert J DeVita, PhD, at the Icahn School of Medicine at Mount Sinai, New York, USA as a new grant for the project entitled: "Substrate reduction as a novel therapeutic strategy for propionic acidemia."
- Awarded $1,890 grant to Community Health Clinic in Topeka, Indiana, USA to perform genetic testing for c.1606A>G in the Old Order Amish (OOA) community.
- Awarded $51,500 grant to Guofang Zhang, PhD, Duke University, Durham, North Carolina, USA as a continuation grant for the project entitled: "Propionyl-CoA and propionylcarnitine mediate cardiac complications in patients with propionic acidemia"

Support Activities

- In October 2020, PAF held a virtual "Family Day" with speakers from the National Institutes of Health, Bethesda, Maryland, USA and Boston Children's Hospital, Boston, Massachusetts, USA. Video recordings of two of the speakers are available for families to view on-line.
- Distributed fall and spring newsletters to affected families, clinicians, and donors
- Coordinated the Propionic Acidemia Foundation's Warrior Birthday Club in which students and staff at Oak Lawn Hometown Middle School and St. Linus School, Illinois, USA make birthday cards for those affected by PA, their siblings, and children.
- Hosted "Fun times with Shayna", virtual dance parties and art classes over Zoom.

Registry

114 Participants in the PA International Patient Registry. The Registry is an IRB-approved research project and the data collected will help characterize the condition of people living with PA.

Publications on PAF funded grants

Alonso-Barroso E, Perez B, Desviat LR, Richard, E. (2021) Cardiomyocytes Derived from Induced Pluripotent Stem Cells as a Disease Model for Propionic Acidemia. *International Journal of Molecular Science.* 22:1161. doi:10.3390/ijms22031161

Fulgencio-Covián A, Álvarez, M, Pepers, BA, López-Márquez A, Ugarte, M, Pérez B, van Roon-Mom WMC, Desviat, LR, Richard, E. (2020) Generation of a gene-corrected human isogenic line (UAMi006-A) from propionic acidemia patient iPSC with an homozygous mutation in the PCCB gene using CRISPR/Cas9 technology. *Stem Cell Research.* 49:102055. doi:10.1016/j.scr.2020.102055

Park KC, Krywawych S, Richards E, Desviat, LR & Swietach. (2020) Cardiac Complication of Propionic and Other Inherited Organic Acidemias. *Frontiers in Cardiovascular Medicine.* 7:617451. doi:10.3389/fcvm.2020.617451

Saleemani H, Egri C, Horvath G, Stockler-Ipsiroglu S, Elango, R. (2021) Dietary management and growth outcomes in children with propionic acidemia: A natural history study. *JIMD Reports.* doi:10.1002/jmd2.12234

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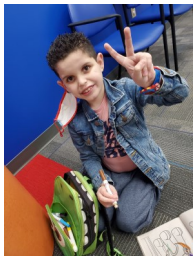
DIEGO'S STORY



Diego is a 12 year old shining boy that got diagnosed with Propionic Acidemia at birth by newborn screening in Puerto Rico.

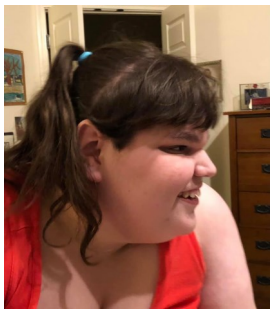
His first 4 years were so hard. We literally lived in hospitals, lots of metabolic crisis including high ammonia levels, high ketones, low sugar, dehydration, loss of appetite, nausea, and vomiting. All of that made him have some growth and developmental delays, low muscular tone, speech disorders, and behavioral issues.

We moved to Florida in 2017, where he started getting better treatment for his disease and a year later, he got his G tube to help him with his calories and nutrients intake. That is when we started to see a big change in Diego's height, weight and development. Right now we are living in Georgia and Diego loves it. Maybe it is because we live by the forest and it gives us a feeling and the mood of our lovely hometown. He feels like home here… and it is.

In the last 7 months, Diego has grown 6 inches and gained 25 pounds. You can see how happy and healthy he looks in pictures, and in real life he just dances, laughs and lives. Well, he is at "that age", a teenager transition, and with PA, his emotions are all over the place. So as happy you can see him, he can also get so frustrated and emotional with situations that he cannot understand or explain. That has been the hardest part recently. It needs patience, love and lots of breathing.

But he makes it through…and then he dances again like nobody is watching. Or maybe he goes to his playhouse and plays with Legos and his favorite toys - Dinosaurs. And his world is perfect again. People that get to know him in person can tell that Diego is the happiest kid in the world, and if you are around him you can feel the magic and the miracle of living in a world full of hope.

IN MEMORY OF PA FRIENDS



Kristin Boecker September 28, 1999 – October 5, 2021

Kristin Rachel Francis Boecker, age 22, slipped peacefully into the arms of her Heavenly Father after fighting a lifelong battle with propionic acidemia. During her life Kristin overcame many obstacles of physical and mental disability and loved life in her world to the fullest. Kristin was such a happy child and wanted everyone to be together, to cook and play with her cars, talking animals or puzzles. For Kristin each day was a beautiful day and her smile brought joy to all those around her. Kristin loved the outdoors, the country, and especially trips to the beach to feel the sea breeze on her face and to listen to the seagulls. Kristin was surrounded by many animals at home which she adored. Her labradors kept an ever watchful eye on her and were rarely out of sight. She was a big fan of Clifford, Elmo, Blues Clues, Little Bear and swinging a glowing light saber. Being quite musical, Kristin enjoyed the piano, drums, the accordion and humming tunes, but Kristin's favorite activity was watching and listening to her favorite U2 concert, the louder the better. We love you Kristin, you will always be our Turtle Girl.

Nicholas Joseph DiMaggio June 16, 2000 - September 12, 2021

Nic, was, without a doubt, the sweetest child this world could ever ask for. He was persistent when it came to helping people figure out what how was telling them. He was passionate about expressing his stories through art drawn by those who adored him. Nic had thousands of drawings created and kept a some on his wall beside his bed and on his ceiling. He loved his Santa and kisses on the cheek from Mrs. Claus, swimming, shopping, going to stores, the library, and grandma's house, Halloween, Christmas, taking walks to find the ice cream truck, painting and most recently coloring his own pictures. Nic lived life with pure joy and happiness, never letting his disabilities gets in the way. He had an extreme love for the people in his life, which includes his family, friends, and caregivers, and was always asking for them to feed his belly and watch his shows with him. He loved watching, Wee Sing, Barney, Sesame Street, Dora and Diego, Blue's Clues, The Wiggles, Teletubbies, and Team umizoomi. Nic made a lasting impression on the lives of all who knew him.

Zachary Jay DiMaggio June 16, 2000 - September 14, 2021

Zac was, without a doubt, the friendliest child this world could ask for. He was always "waiting or counting Down" the days to see his special people and make-believe places. He was passionate about doing puzzles, especially from pictures he took on his Ipad. He loved all things purple and his shows, especially Barney. He was barney's # 1 fan. Zac enjoyed baths in his mommy's tub, grandma's house, snow, bubbles, helium balloons, golf cart rides with dad, dancing, Halloween, Christmas, and he couldn't get enough of his computer. He loved his shows. Zac lived his life with pure joy and happiness, often hugging his caregivers, friends, and family with his famous headlock style hug. He had an extreme love for the people in his life. Zac made a lasting impression on the lives of all who knew him.

MUHAMMAD WASIQ'S STORY

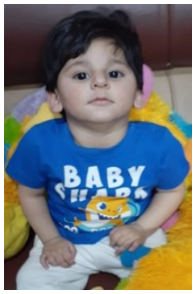
JOURNEY OF MUHAMMAD WASIQ

(DoB: 17 May, 2019) - Islamabad, Pakistan

Metabolic Disorder – Propionic Acidemia

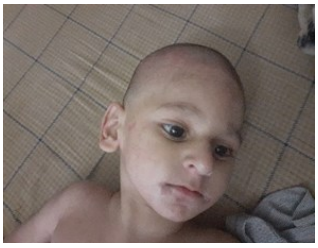
Muhammad Wasiq born on 17 May 2019 in capital of Pakistan in an economically strong family. After few initial days care in one of the most equipped private hospital in Pakistan, he began to grow well without any complication. Wasiq was active, happy and a healthy child and his parents used all best parenting practices learning from his elder two brothers, brought up specially in diet. Wasiq was active than any other child at the age of seventh months.

At seventh month, Wasiq suffered high fever for continuous eight days after which his health started to decline. In those months, he also had mild constipation at random intervals. Days came when his constipation and vomiting extended to a spell of eight days. Medical tests verified Propionic Acidemia (PA) at 12th Month. These tests are done in Pakistan in only one hospital at Karachi city. After that, every day turned out to be a challenge for the family.



Pakistan is a country where pre marriages medical genetic tests are discouraged. Health budget is not enough to respond to national needs. Private medical facilities are preferred over Government services. Screening and by birth medical tests facilities are not available in country. As a result, there are multiple medical issues spread out in country. COVID-19 had devastating impact on medical and economic conditions in country with complete lock downs and situation further deteriorated.

When Wasiq was diagnosed with PA, we were informed about the damage already done in brain by protein intake. He could not sit, speak and had wavy body movement. We needed medical advice but due to the fact that PA cases are very rare in Pakistan, we struggled to seek medical advice despite of reaching out to best hospitals in country. Until one day, we found a doctor who is the only expert in metabolic disorders in country. After couple of advices through virtual meetings, we travelled to Karachi to meet her face to face. Doctor adjusted our diet with medicines to control ammonia level. We controlled his diet and gave medicines. Soon in this phase, Wasiq started to show rashes on face and on his back which was clear indication of protein deficiency. The problem was that we were following and implementing doctor's advised plan but struggled to achieve nutritional diet balance and we needed further advice.



On extensive search to solve this issue, we connected with a nutritionist who was keen to connect and had interest in metabolic probes. We shared the diet plan and medicine package with nutritional expert who readjusted the whole package and we started to see improvement in child condition. Wasiq was much stable now and now came the rehabilitation phase by assessing his complete body functions. Emphasis focused on physiotherapy, occupational and speech therapy with further confirmation of hearing loss. He can now sit with support and can move his feet with support if brought in standing posture however the backbone imbalance and jerky movement does not help much to stable him.

Present challenge is to find food and medicines which are often not available in city. Searching, tracing, order and delivery from other city take time and resources. As we know PA child follow vegan diet line but it also needs nutrients to bring diet balance, substitute formulas are hard to find. There is only one importer in country and because data of such children is not available, need & supply balance is always out. Consequently, every day is a challenge.

There is a lot to be done for such children. Families of metabolic disorders have now connected through social media to help each other and extend help to meet daily needs. Country like Pakistan where infrastructure is not strong, help comes through social support of interconnected communities through welfare initiatives. Children like Wasiq are extending help to other needy children on weekly bases by sharing food and by supporting financially. The issue is taken up collectively by parents to government authorities and escalated on local media. Substantial action is awaited. Every day passes with a hope that the voices will be heard soon to get consistent support.

Written on 2nd May, 2021 by father Saqib Javed, Pakistan

(SJQMZD@GMAIL.COM)

We want to hear from you!

Have a PA story to tell, event to promote or news?

Spring newsletter submissions due by February 1, 2022.

PAF EVENT & FUNDRAISING SPOTLIGHT

PAST EVENTS

- **Fall 2021 - 16th Annual Tailgate Party & Corn Hole Tourney for PAF (Virtual)**, Raised $7,000+
- **Oct. 2021 —Meigs High School UNICEF, Corn Hole Tourney for PAF,** raised $915+
- **October & Ongoing—Pounding the Pavement for PAF:** Robert Tobias, Maria Cotrina

GIFT MATCHING: This may enable you to double your donation. Check with Human Resources to see if your employer matches. It makes a big difference.

FACEBOOK: Thank you to all of our Facebook Fundraisers and people that donated to their fundraising pages for birthdays, #GivingTuesday or just because: Sonia Phillips, Robert Kiante, Salli-Silverback Koncher, Lisa Shutts-Mash, Gabriell Snyder, Amy Wilson

STOCK DONATIONS: PAF is now accepting stock donations. Please email paf@pafoundation.com with any questions.

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**: Allison Ellis, Kate Lowry, Gwen Mouat, Trent McKinley, Salli Silverback Koncher
- **In Memory Of**: Kristin Boeacker, Vincent Philip Franze, Jordan Franks

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.

INTERNET
Thank you for using Igive, Goodsearch and AmazonSmile and designating Propionic Acidemia Foundation as your charity and setting up Facebook Fundraising Pages. Every dollar counts.

Thank you for making a difference.

SUBSTRATE REDUCTION: NOVEL THERAPEUTIC STRATEGY FOR PA

PAF Funded Grant titled "Substrate reduction as a novel therapeutic strategy for propionic acidemia" receives NIH funding

PI: Sander Houten, Ph.D., Department of Genetics and Genomic Sciences, Icahn Institute for Data Science and Genomic Technology, Icahn School of Medicine at Mount Sinai, NY, US
Co-PI: Robert J. DeVita, Ph.D., Department of Pharmacological Sciences, Drug Discovery Institute, Icahn School of Medicine at Mount Sinai, NY, US

In January 2021, we were lucky to receive a research grant from the PAF, which allowed us to start the development of pharmacological substrate reduction as a novel therapeutic strategy for propionic acidemia. For this project, we hypothesize that we can achieve a clinically relevant reduction in the accumulation of propionyl-CoA carboxylase substrates by inhibiting enzymes that play a role in the degradation of branched-chain amino acids. Specifically, we propose to inhibit short/branched-chain acyl-CoA dehydrogenase (SBCAD) and isobutyryl-CoA dehydrogenase (ACAD8), which are involved in isoleucine and valine degradation, respectively. Inhibition of these enzymes is thought to be safe because in contrast to propionic acidemia, inherited defects of SBCAD and ACAD8 are thought to be benign conditions. In cell line models, inhibition of SBCAD using a genetic KO or an inhibitor was efficacious and led to a pronounced decrease in the propionyl-CoA carboxylase substrate. The goal of the project is to identify small molecule inhibitors of SBCAD and ACAD8 that can be further optimized and serve as a starting point for a broader translational drug discovery program for treatment of propionic acidemia. In order to achieve this goal, we used the research grant from the PAF to develop the assays necessary to establish if a small molecule is an effective SBCAD or ACAD8 inhibitor. We have also performed a virtual screening and have a list of candidate inhibitor molecules.

This progress enabled us to propose this research project for the NIH Small Grant Program (R03) of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). This grant was awarded in September, which will allow us to continue this work for the next 2 years, and we hope to keep reporting the outcomes of our studies to the PAF.

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, P.O. Box 151, Deerfield, IL 60015-4421. If you would like to be removed from our mailing list or receive the newsletter via email, please contact us.*

PA mouse model Patient Summary

Patient Summary of "Pantothenate kinase activation relieves coenzyme A sequestration and improves mitochondrial function in a propionic acidemia mouse model"

New data published by our scientific collaborators at St. Jude Children's Research Hospital in Science Translational Medicine describe the effect of PZ-3022 in a mouse model of propionic acidemia (PA).

Individuals with PA cannot break down parts of protein and some types of fat due to either a missing or a non-functioning enzyme called propionyl-CoA carboxylase (PCC). When this enzyme is not working properly, there is thought to be a shortage of coenzyme A (CoA), resulting in cells in the body being starved for energy.

PA mouse model

In this paper, the scientists used a mouse model of PA that have a PCC enzyme which is mostly non-functional. Thimouse model was originally developed by Dr. Michael Barry's laboratory at the Mayo Clinic in 2016. In prior studies it has been established that, these mice have changes in biomarkers including high levels of C3-carnitine and an elevated C3:C2 carnitine ratio in blood samples and in the liver, similar to PA patients. Furthermore, the PA mice experience heart complications, similar to some PA patients, including increased heart weight compared to healthy animals.

Treatment of a PA Mouse Model with PZ-3022 Improved Aspects of Disease

For the first time, the authors of this paper characterized CoA in these PA mice. They observed a shortage of free CoA (CoASH) and C2-CoA in the liver, supporting the idea that CoA depletion occurs in this disease. PZ-3022 increased free CoA (CoASH) and C2-CoA in the liver of PA mice compared to untreated mice. Treatment of PA mice with PZ-3022 also reduced C3-carnitine and the C3:C2 carnitine ratio in the liver and reduced the C3:C2 ratio in plasma. Overall, these data suggest that PZ-3022 treatment improved the metabolic state of the PA mice.

Previous work by other scientists suggests that mitochondria, the "powerhouse" of the cell, do not function properly in PA. The Tricarboxylic acid cycle, (TCA cycle; also sometimes called the Krebs cycle or citric acid cycle) is a series of chemical reactions in mitochondria that cells use to break down organic fuel (sugars, fatty acids, and some amino acids) to harvest energy for cells. In this paper, our collaborators at St. Jude show that TCA cycle intermediates (chemicals in these reactions) are elevated in the blood and urine of PA mice compared to healthy mice, suggesting the mitochondria are not working properly. PZ-3022 reduced the high levels of TCA cycle intermediates observed in the plasma and urine of PA mice, suggesting that PZ-3022 treatment improves mitochondrial function in PA mice.

CoA Therapeutics is developing a similar compound, BBB-671, an oral therapy currently under investigation in a Phase 1 study (NCT04836494) in healthy volunteers and patients to assess safety and determine an appropriate dose..

Supported by CoA, a BridgeBio company.

HERO Clinical Study Recruiting Participants

The HemoShear Therapeutics **HERO** (**HE**lp **R**educe **O**rganic Acids) clinical study is recruiting participants at several leading children's hospitals across the United States.

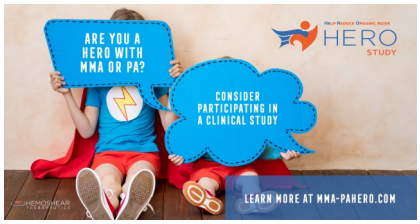
The study is enrolling children and adults with MMA (mutase deficient) and PA aged 2 and older who meet the study criteria.

The HERO study will assess the safety, effectiveness and metabolism of HST5040, an oral investigational drug developed by HemoShear to potentially reduce the toxins that cause harm in MMA and PA patients. HST5040 has the potential to be active throughout the body, including the brain, heart, liver, kidneys and muscles.

The investigational drug can be taken conveniently at home as a daily liquid formulation by mouth or through a gastric feeding tube. Study participants will have the opportunity to continue to take the drug until it is approved for use or the study ends.

You can learn more about the study at MMA-PAHero.com

The safety and effectiveness of HST5040 for the treatment of MMA or PA have not been established.



Searching for a Cure
Hope for Our Children

Propionic Acidemia Foundation
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PAF volunteers and board members are needed!

paf@pafoundation.com