SEARCHING FOR A CURE HOPE FOR OUR CHILDREN

Propionic Acidemia Foundation

VOLUME 1, ISSUE 27 FALL 2019

PAF Reaches $1,000,000 for Research

Thank you to all of our families, friends, and donors for helping us reach this milestone. Due to your generosity, we have distributed $1,000,000 for research. Projects that have been funded include gene therapy, enzyme replacement therapy, chaperones, studies on basic science of PA, studies on heart and brain involvement, looking at the pathways, and the PA International Patient Registry to name a few. A complete list can be found on our website.

Most PAF grants are $50,000 or less per year for the researchers with the hope that enough data will be generated for them to apply for large grants with PAF or other institutions.

This October we received five grant requests which are being evaluated by our Medical Advisory Board. In addition, there are three projects that will be finishing their first year of funding and eligible to apply for an additional year of funding. Thank you for helping PAF do what we do. We couldn't do it without your support. —Your PAF Board

Gwen's Story

Gwen turned 13 in February 2019 and just started her 7th grade school year. During her early years we never expected she would celebrate this birthday, nor did we have any idea what a full and amazing life she would live. She's a ray of sunshine every single day. Gwen doesn't appear to feel anger or hate, which makes her life truly amazing. To her, everyone is good and everything is sunny (except for blood draws and spiders).

Gwen became very ill at two days old and was admitted to Nationwide Children's Hospital NICU. She was placed on a ventilator and received peritoneal dialysis for a couple of days until she came out of her coma and was breathing on her own. (Continued on page 6)

PA Registry

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

As of October 1, there are 104 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.

GENE THERAPY & OTHER APPROACHES TO CURE PA

Understanding the different strategies with potential to cure PA by M. L. Cotrina, PhD

What is gene therapy and how does it work?

The term "gene therapy" is applied to any strategy that introduces a healthy gene into the organism to replace a defective one. For this to happen, it needs to be ensured 1) that the gene that is introduced travels to the correct organ and then to the correct area in the cell before it starts working; 2) that once the "good" gene arrives to the right cell and organ, it starts making the right protein and 3) that the right amount of the good protein is made so that it can start functioning efficiently in the body.

Why is "gene therapy" important to cure propionic acidemia?

In propionic acidemia, the gene that contains the information needed to metabolize (or break down) some amino acids and fats is defective. This gene is called PCC (propionyl -CoA carboxylase) and is formed by two different elements: PCCA and PCCB. Some children are born with defects in the PCCA element or the PCCB element or in both. Thus, introducing a healthy PCCA or PCCB into the body should, in principle, lessen the effects or even cure the deficits created by the mutated PCC DNA.

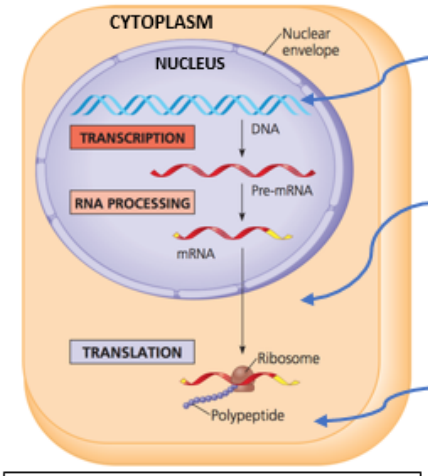


Diagram of a human cell with the central dogma: from DNA to RNA to protein (adapted from Campbell Biology, Pearson)

Is gene therapy the only way to cure propionic acidemia?

No. Gene therapy works at the level of the DNA: it introduces the correct gene for the PCC protein to be properly made. However, the correct protein can also be made up if we introduce the intermediary step, the mRNA. The main difference here is that the mRNA acts as if it were a traditional medication, "taking" it as needed. By contrast, the introduction of the DNA is more permanent, altering the genetic information at its core. Another difference is that mRNA is "ready to go": it can start producing protein in the cytoplasm right away. By contrast, DNA needs first to go to the nucleus of the cell, be transcribed into mRNA, and then be transported into the cytoplasm to make protein.

What therapies are currently being developed to treat propionic acidemia?

Right now, there are three main approaches being investigated to treat propionic acidemia or its related disorder, methylmalonic acidemia (MMA):

-**mRNA injections**. introduction of the mRNA into the body so that it can make the PCC protein. This strategy will require multiple injections of mRNA to produce enough PCC protein. It would have effects similar to a liver transplant with less risk.

-**Adenovirus mediated gene therapy**. This approach involves a virus that can be linked to other pieces of DNA, in this case, the healthy gene for PA. The virus has been altered such that it is safe and enters into the liver. This treatment is more stable than mRNA because, whereas mRNA can be destroyed in the cell after some time, the virus and the gene that it carries enter the cell nucleus and become part of the cell's DNA, where it can be read as many times as needed.

-**Chemical compounds**. Similar to a conventional medication, these compounds are molecules that could improve cell metabolism even when the cells have a defective PCC. These molecules are being investigated in "artificial" livers, heart cells and even in whole animals like fish. If one effective compound is found, it will need to be developed for human testing.

Has gene therapy cured other human diseases?

Yes. Since 2016, six gene-therapy products have been approved worldwide.

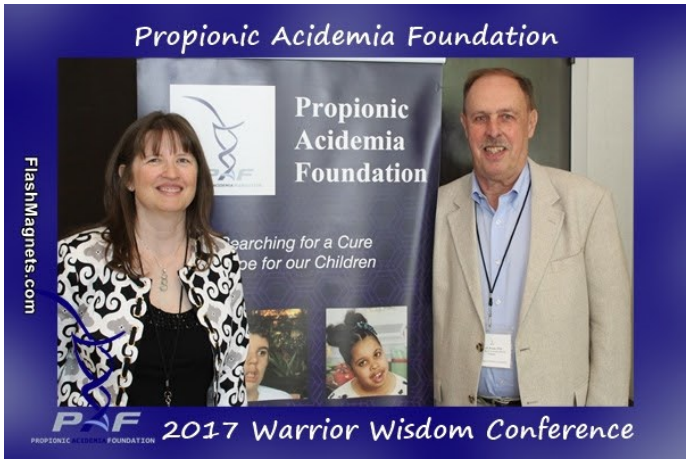
There are now more than 800 cell- and gene-therapy programs in clinical development for a series of untreatable diseases.

(continued on page 4)

Tribute to Jan Kraus

The PA community was saddened to hear of the passing of Dr. Jan P. Kraus, emeritus professor of Pediatric-Clinical genetics and Metabolism at the University of Colorado, on July 3rd. Dr. Kraus dedicated his life to research of Propionic Acidemia and Homocystinuria.

He received several research grants from the Propionic Acidemia Foundation. He discovered the enzyme structure of propionyl CoA carboxylase and his lab has maintained a database of the various PCCA & PCCB mutations. He presented at and attended many Propionic Acidemia Foundation conferences. At the 2013 conference in Colorado, he gave a tour of his lab to conference attendees. Dr. Kraus was more than a researcher to the PA community, he was family. He will be missed and remembered.



17th Abbott Metabolic Conference: Advances in Management of Inherited Metabolic Disorders

Memphis, TN May 30-June 1, 2019
By Brittany S Smith, PAF Board Member & Treasurer

PAF had a table at the 2019 ABBOTT Metabolic Conference. There were several presentations and debates that were relevant to the PA community. The first was Dr. Sufin Yap, MD, from Sheffield, UK, who spoke on Organic Acidemias. She described how she has observed her patients in a metabolic crisis and that their livers can enlarge very rapidly. Dr. Yap also described how she has used Carbaglu within a crisis situation and it has brought the ammonia levels down on her patients. The medication was also shown to improve the quality of life of patients with PA using the medication, this was shown by using the PedsQL, a quality of life survey tool. Carbaglu has been used in Europe for over 15 years.

Three dietitians gave a joint presentation on Emergency Preparedness, detailing the impacts of natural disasters on the clinics and staff and also families serviced by their clinics. Amy Cunningham, RD; Suzanne Hollander, RD; and Heather Saavedra, RD, each detailed natural disasters they have had in their areas of the country, which have included wild fires, hurricanes, flooding, droughts, and earthquakes. They have not only impacted families, but the clinic operations. In some cases the hospital and clinics were closed for months. Families, too, were significantly impacted and in one case, a family utilizing one of the clinics had only 5-10 minutes to flee their home. Overall, they indicated a need for all of the metabolic clinics and newborn screening offices to create Emergency Preparedness plans, as well as, helping affected families to prepare as well.

The last session that I wanted to mention was a debate session in which a team of doctors and dietitians each had to debate one side of a treatment suggestion. One was on liver transplantation and whether to encourage or discourage a metabolic family to investigate liver transplantation. While the debate was interesting, the discussion that followed was poignant; they were open to being corrected if they had misstated facts, one being using the livers from those with PA and UCDs in a "domino" transplant, and the other was that they all recommended encouraging their families to seek out information and go down a treatment route if the parents felt that was what was best.

GENE THERAPY & OTHER APPROACHES (CONT. FROM PG. 2)

Scientists and pharmaceutical companies are only beginning to establish how many disorders can be treated with gene therapy, how many injections will be required for an effective therapy, and how much these therapies will cost. It must not be forgotten to apply caution to guarantee the safety and affordability once these therapies reach the patients.

Additional sources of information:

-Keener AB. Just the messenger. Nat Medicine.2018. https://doi.org/10.1038/s41591-018-0183-7

-High KA and Roncarolo MG. Frontiers in Medicine: Gene Therapy. N Engl J Med 2019;381:455-64. DOI: 10.1056/NEJMra1706910

GLOSSARY

Gene – genes contain genetic information, the code or instructions necessary to form the whole human body and make it function. Genes are composed of molecules called DNA (deoxyribonucleic acid).

Proteins - Proteins are composed of chemicals called amino-acids. DNA by itself does not carry out any particular function, like transporting oxygen in the blood or contract the muscle to produce movement. But proteins like hemoglobin in blood or tropomyosin in the muscle can. DNA is like the instruction manual for how the body is supposed to work. Proteins are like the architects and crew that carry out the instructions from this manual.

mRNA- The instructions found in DNA are not directly read to form proteins. There is an intermediary molecule between DNA and proteins called mRNA (messenger Ribonucleic acid).

Transcription – the process by which DNA is read into mRNA

Translation - the process whereby mRNA is read into proteins.

Cytoplasm/Nucleus – different compartments within cells. The nucleus contains the DNA whereas the cytoplasm is the region where proteins are made.

RESEARCH GRANT UPDATE - EVA RICHARD, PHD

Cardiomyocytes derived from induced pluripotent stem cells as a new model for therapy development in propionic acidemia

Eva Richard, PhD
Centro de Biología Molecular "Severo Ochoa"
Universidad Autónoma de Madrid

There is an unmet clinical need to develop effective therapies for propionic acidemia (PA). Advances in supportive treatment based on dietary restriction and carnitine supplementation have allowed patients to live beyond the neonatal period. However, the overall outcome remains poor in most patients, who suffer from numerous complications related to disease progression, among them cardiac alterations, a major cause of PA morbidity and mortality. In our research, we developed a new cellular model of PA based on induced pluripotent stem cells (iPSC) with the goal of defining new molecular pathways involved in the pathophysiology of PA which would be potential treatment targeting.

Traditionally, disease pathophysiology has been studied in immortalized or human cell lines and in animal models. Unfortunately, immortalized cells often do not respond as primary cells and animal models do not exactly recapitulate patients' symptoms. So far, patients-derived fibroblasts have been mainly used as cellular models in PA due to their availability and robustness, but they have important limitations.

The ability to reprogram somatic cells to iPSCs has revolutionized the way of modeling human disease. To study rare diseases, stem cell models carrying patient-specific mutations have become highly important as all cell types can be differentiated from iPSCs. We have generated and characterized two iPSC lines from patients-derived fibroblasts with defects in PCCA and PCCB genes. These iPSC lines can be differentiated into cardiomyocytes that mimic the tissue-specific hallmarks of the disease. The presence of PA cardiomyocytes has been easily established by visual observation of spontaneously contracting regions, and the expression of several cardiac markers. We have observed that PCCA-deficient cardiomyocytes present an increase in degradation products and in lipid droplets, and exhibit mitochondrial dysfunction compared to control cells. We further discovered the down-regulation of several miRNAs in PCCA cardiomyocytes compared to control ones, and several miRNAs targets are currently being analyzed in order to investigate underlying cellular pathological mechanisms. Interestingly, we have performed several experiments to analyze the effect of the mitochondrial biogenesis activator, MIN-102 compound (PPAR agonist, derivative of pioglitazone) in cardiomyocytes. Preliminary results showed an increase in the oxygen consumption rate of PCCA and control cells. In our next steps, we plan to complete the analysis in the PCCA cardiomyocyte line, characterize PCCB cardiomyocytes and to study in depth the therapeutic potential of MitoQ and MIN-102 compounds.

We would like to sincerely thank the Propionic Acidemia Foundation for supporting our research.

Walk For A Redhawk

By Maddy Engles

On April 23, 2019, the Naperville Central High School community joined together for "Walk For A Redhawk" to honor Talli Smith, who had passed away from Propionic Acidemia in February. The event was put together by Drilona Ibraimi, Smith's daily nurse.

"I decided that we had to put something together in memory of Talli because I knew the impact she had on each and every person she met throughout her life, and anyone who knew Talli knows that she would be the first person to be involved in putting something like this together for someone else. She was just ecstatic about helping others", Ibraimi said.

Ibraimi designed and ordered pink "Walk For A Redhawk" t-shirts and wristbands, which were sold by Talli's Adapted P.E. tribe, her family, and retired P.E. teacher Mrs. Adamatis throughout the school and community for two weeks leading up to the event.

On the day of the walk, Naperville Central students wore their shirts during the school day and met after school to embark on a walk to the Downtown Naperville Riverwalk, ending at the Bell Tower with an energetic dance party. "We danced, sang, and laughed the whole time. It was a perfect way to celebrate one of the most amazing young girls I have ever met, all while supporting other kids with PA", said Ibraimi. Afterward, the Naperville community met at a local Chipotle to eat dinner, with a portion of the proceeds going to the PA Foundation.

The "Walk For a Redhawk" was overall an event filled with laughter, love, and joy: it was just how Smith lived her life. As a whole, the day raised $8,501.82. However, it meant more than just money. It kept Talli's memory alive and honored her fight against P.A. Naperville Central alumni, Jenna MacLaughlin, who was in Smith's tribe, was very pleased with how the event went, along with the rest of the community.

"Coming to the walk and seeing how many people wanted to support not only Talli, but her family, friends, and the Propionic Acidemia Foundation was truly heartwarming," MacLaughlin said. "Everyone had tons of fun socializing, reminiscing, singing, and dancing; which was what Talli would have wanted!"

PROP Toolkit is Now Available

On behalf of Rani Singh, PhD, RD and Fran Rohr, MS, RD and the PROP Toolkit Workgroup; we are pleased to announce that the Propionic Acidemia (PROP) ToolKit is now available online. The PROP toolkit consists of 11 case scenarios detailing nutrition intervention for newly diagnosed infants, children, teenagers and pregnant women living with Propionic acidemia.

The PROP toolkit may be found via the following weblink: https://southeastgenetics.org/ngp/toolkit_prop.php

The PROP Toolkit is an international collaborative project, including case contributions from experienced metabolic dietitians working in the US, Canada, and Mexico. We hope the PROP Toolkit case examples as an adjunct to the PROP Nutrition Guidelines will be helpful to metabolic dietitians providing medical nutrition therapy for individuals living with propionic acidemia.

Thank you for your continued support and participation in this project. We always appreciate your feedback. Please let us know if you have any questions and/or comments.

Sincerely, Keiko and Elaina
Co-chairs, OA Workgroup/PROP Toolkit Workgroup
SERN-GMDI Nutrition Guidelines project
Co-PIs: Rani Singh, PhD, RD, LD and Fran Rohr, MS, RD
GMDI President: Mary Sowa, MS, RD

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. Please sign up a patient or sibling for the Warriors Birthday Club 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.

PAF EVENT & FUNDRAISING SPOTLIGHT

UPCOMING/ONGOING EVENTS

- **Dec. 3- Giving Tuesday,** Celebrated on the Tuesday following Thanksgiving (in the U.S.), Giving Tuesday kicks off the charitable season, when many focus on their holiday and end-of-year giving. One of the best ways to get involved is by donating to Propionic Acidemia Foundation.

PAST EVENTS

- **14th Annual Tailgate Party & Corn Hole Tourney for PAF**, Gahanna, Ohio
- **Team PA Runners, Nationwide Children's Hospital Columbus Marathon, Ohio**

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.

INTERNET

Thank you for using Igive, Goodsearch and AmazonSmile and designating Propionic Acidemia Foundation as your charity

FACEBOOK: Thank you to all of our Facebook Fundraisers and people that donated to their fundraising pages: Thank you for making a difference. Sonia Phillips Birthday Fundraiser, Grace Lendzion, Tahirah Anderson's Birthday Fundraiser, John Moss's Fundraiser, Kierstin Berg's Birthday Fundraiser

STOCK DONATIONS: PAF is now accepting stock donations. 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**: Trent McKinley, Chase Workman's Graduation, Kate Lowry, Michael J. Messersmith
- **In Memory Of**: Larry R. Stecken, Jordan Franks, Kirstyn Tripp, Talli Smith, Cady Pierce, Connor McKillop, Nicholas Phillips, Vincent Franze, Sean and Courtney Callahan
- **In Memory of Talli Smith**
  -Naperville 203 Connections- $175.11
  -Walk for a Redhawk, Remembering Talli- see pg. 5)
  -NCHS 2019 Class Donation, In Memory of Talli- $3,000

PA RUNNER UPDATE

Support the effort to improve treatments and create new therapies for PA or join the 2019 team with a distance and race of your choice. All abilities welcome!!! Contact Marisa Cotrina for more informationteamPAR4@gmail.com

GWEN'S STORY (CONT. FROM COVER)

On her third day she was diagnosed with PA. At age 1 she stopped eating by mouth and since then she's been 100% by a feeding tube because she refuses to eat. Despite that setback, she continues to grow and thrive. Last year, during a visit to NIH, she was officially diagnosed with a mild form of autism.

Gwen is a huge fan or talking, singing, dancing, and playing with her dolls. She loves beach vacations and trips to Disney World; her favorite ride is Hollywood Tower of Terror. In 2015 she joined the local Special Olympics swim team and is now on their gymnastics team as well. Until August of this year, Gwen had nursing care Monday-Friday. This school year we made the tough decision to eliminate her in-school nursing care. It's been a big transition but she's handled it very well so far. She rides the bus to school on her own, transfers classrooms, goes to the nurses office for lunch (tube feedings), and rides the bus home where her brother Robbie (16) greets her. Until I'm home from work, she does homework and reads. Right now she's really into *Frozen* chapter books.

Speaking of Frozen, this past spring, Gwen begged to audition for *Frozen Jr.*, a musical for kids 13 & under. She went into the audition room on her own (dressed as Anna), sang "Do You Want To Build A Snowman", read lines with the casting team, and landed a small part as Middle Elsa! It was a dream come true for her. After 3 months of practices, she made her stage debut in June. She had 7 costume changes, 3 dance numbers, several lines, and even a little solo. It was truly amazing.

Gwen struggles to make friends her age, which is tough with her being in middle school, but it doesn't seem to bother her. She's mostly drawn to befriending preteen girls and avoids talking to boys. While she's missing out on many of the social things that typical middle school kids do, she's constantly finding new ways to fill those gaps. Her journey so far has been one of a kind and full of happiness. Is there anything better than that? For more on Gwen's story, visit GwenForACure.com.

FINANCIAL REPORT

	Revenue:
Contributions.....	$154,022
Interest & Royalty Income.....	$ 10,126
Program Revenue.....	$ 19,582
Total Revenue.....	$183,730
Expenses:	
Program service.....	$104,458
Management & General.....	$ 2,365
Fundraising.....	$ 728
Total Expenses.....	$107,551
Cash Assets 8/01/2018.....	$383,550
Cash Assets 7/31/2019.....	$459,731

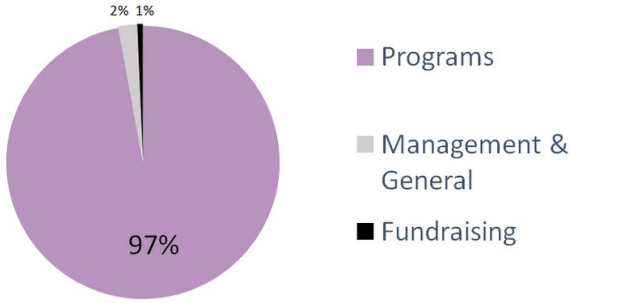
BOARD OF DIRECTORS/OFFICERS

Jill Chertow Franks, President
Brittany Smith, Treasurer
Angela Waits, Secretary
Ann Marie Young
Maria L. Cotrina

Board Disclosure:
Donations made by board members totaled $125

PROGRAM ACCOMPLISHMENTS

- Awarded research grant to Guofang Zhang, PhD, Duke University: "Propionyl-CoA and propionylcarnitine mediate cardiac complications in patients with propionic acidemia."
- Awarded research grant to Eva Richard, PhD, Universidad Autonoma de Madrid, Spain: "Cardiomyocytes derived from induced pluripotent stem cells as a new model for therapy development in propionic acidemia."
- 104 Participants in PA Patient Registry
- Distributed fall and spring newsletters to affected families, clinicians, and donors
- Attended and exhibited at Abbott Nutrition Metabolic Conference-Memphis, TN
- Attended and exhibited at Society for Inherited Metabolic Disorders 41st annual meeting- Seattle, Washington. Board Member Marisa L. Cotrina PhD shared her poster: "High Incidence of Autism/ASD in Propionic Acidemia: Data from the Propionic Acidemia and Urea Cycle Disorders Registries."



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 10, 2020.

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

Propionic Acidemia Foundation
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Propionic Acidemia Foundation

Join and follow Propionic Acidemia Foundation on Facebook

PAF volunteers and board members are needed!

paf@pafoundation.com

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