SEARCHING FOR A CURE HOPE FOR OUR CHILDREN

Propionic Acidemia Foundation

VOLUME 1, ISSUE 29 FALL 2020

PAF VIRTUAL FAMILY DAY

Saturday, October 24th
10:00 a.m. - 12:00 p.m. (Central Daylight Time)
(3:00 p.m. GMT)

While we wish we could all be together, this meeting will be different. Please join us for our Virtual Family Day. We are happy to be able to make this available to our families from far away in addition to those who are near.

Speakers include:

Benjamin D. Goodlett, PhD
Attending Psychologist, Division of Genetics and Genomics, Boston Children's Hospital; Instructor, Department of Psychiatry, Harvard Medical School

Title: Long-Term Family Plans during COVID-19

Oleg A. Shchelochkov, M.D., FAAP, DABMG
Associate Research Physician, Organic Acid Research Section, National Human Genome Research Institute National Institutes of Health

Title: An Update on the NIH Natural History Study of Propionic Acidemia

Charles Venditti, MD, PhD
Senior Investigator, Medical Genomics and Metabolic Genetics Branch. Head of the Organic Acid Research Section, National Human Genome Research Institute National Institutes of Health

Title: Treatment Approaches to Propionic Acidemia

Registration is free.
Registration information will be available at www.pafoundation.com

PA Registry

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

As of September 15, there are 114 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.

RESEARCH GRANTS UPDATES

PAF Awards $44,253 New Research Grant

Rajavel Elango, PhD., University of British Columbia

"Optimizing amino acids in medical foods to manage propionic acidemia."

Propionic Acidemia (PA) is primarily caused by an enzymatic defect, propionyl-CoA carboxylase (PCC), in the catabolic pathway of valine, isoleucine and other propiogenic precursors. The dietary management of PA mainly depends on protein restriction from food to reduce supply of propiogenic amino acids, and the use of special medical foods. These medical foods contain all essential amino acids and nutrients, but no propiogenic compounds. Recently, concerns have been raised about their use, due to the imbalanced content of the Branched Chain Amino Acids (BCAA) - high leucine, to minimal or no valine and isoleucine. The imbalanced mixture of BCAA negatively impacts plasma concentrations of valine and isoleucine, and has been proposed to affect growth in pediatric PA patients.

In an ongoing retrospective natural history study (n=4), patients with PA treated at our center from birth (or diagnosis) to age 18y, we observed that higher intake of medical food (compared to intact protein) results in lower ht-for-age Z scores. Based on this pilot data, we propose that there is an immediate need to determine the optimal amounts of leucine to be present in the medical foods.

Therefore, the specific objectives of the current study are to:

1. Stable isotope studies

1.1 Determine the ideal ratio among BCAA in children using the stable isotope-based indicator amino acid method to optimize protein synthesis in a Proof-of-Principle approach.

1.2 Test the ratio among BCAA using the same stable isotope -based method in our cohort of PA patients to determine impact on protein synthesis, and plasma metabolite responses.

2. Determine the impact of the use of natural (intact) vs formula (medical food) protein on anthropometric, biochemical and clinical outcomes via a retrospective natural history study of PA patients treated at BC Children's Hospital.

Recent dietary guidelines for PA are discouraging the reliance on medical foods as a sole dietary source. However most individuals with PA are at risk for malnutrition and depend on these medical foods as an easy tolerable source of energy and protein. Thus, determining the optimal ratio of BCAA in PA medical foods is necessary to optimize protein synthesis, promote anabolism, growth and prevent the accumulation of toxic metabolites.

Our laboratory, equipped with use of novel stable isotope tracers to examine protein and amino acid metabolism, is ideally suited to address the question of the ideal BCAA ratio to be used for dietary management of PA and potentially impact health outcomes.

PAF Awards $50,000 New Research Grant

Ken Maclean, PhD, University of Colorado Denver

"Chemical Chaperone Treatment to Restore Enzyme Activity in Folding Mutations of Propionyl-Co-A Carboxylase: Towards a Personalized Therapeutic Strategy in Propionic Acidemia (PA)"

Propionic acidemia (PA) is a severe life-threatening disease for which there is currently no truly effective treatment. The disease is caused by mutation in one of the two genes that code for the enzyme propionyl-CoA carboxylase (PCC). This enzyme is made up of two different proteins that fold around each other into a complex structure with six of each of these two molecules. This is a very unusual and complex structure for a metabolic enzyme and recent work in our laboratory has found that a number of specific mutations that cause PA cause problems by interfering with the protein folding and/or assembly process leading to a non-functional enzyme and thus the disease. In cells, proteins with complicated folding patterns are often assisted in their folding by other proteins called chaperones. We have observed that a number of mutant forms of PCC can be restored to normal

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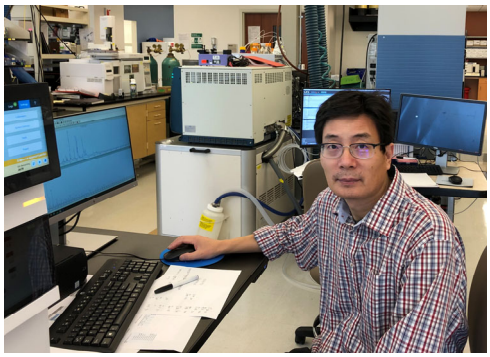
RESEARCH GRANTS (CONTINUED FROM PAGE 2)

activity if they are helped to fold correctly using these chaperone proteins.

In our study, we will examine a number of chemicals that can also function as chaperones and assist with protein folding with a view towards restoring full activity in mutant forms of PCC. This work will initially occur in a bacterial PCC expression system to identify promising compounds and then depending upon progress, move into treating human PCC patient derived cells. These studies have the potential to serve as an initial first step in the rational design of a personalized medicine strategy for patients with specific mutations causing PA.

PAF Awards $51,500 Continuation Research Grant

Guofang Zhang, PhD, Duke University



Cardiac disease is one of complications often associated with propionic acidemia (PA). Understanding the pathological mechanism is essential to prevent the development of complication. Our previous research has shown that propionyl-CoA accumulation inhibits the metabolism of fatty acid which is a major fuel for cardiac energy. The loss of fuel switch flexibility could interfere with cardiac energy metabolism and potentially develop cardiac complications particularly under various stresses. Our research was funded by PAF to investigate the pathological mechanism of cardiomyopathy associated with PA in 2019. In the year 1 of PAF award, we started to map out the metabolic source of propionyl-CoA in heart. Surprisingly, the amino acids (isoleucine, threonine, methionine, valine) and protein which are known to be substrates of propionyl-CoA have negligible contribution to propionyl-CoA production in heart. However, our data does not exclude the possibility that these amino acids substantially contribute to propionyl-CoA production in other organs, like liver. Circulating propionate is a major source of cardiac propionyl-CoA. It also fits the observation that heart prefers fatty acids including short-chain fatty acids as energy substrates. More than 99% propionate originating from microbiome is efficiently removed/ metabolized at its first pass through liver in healthy rodents. Therefore, circulating propionate maintains at very low level after liver. The deficiency of PCC attenuates hepatic ability of disposing propionate and increases circulating propionate level, which exacerbates propionyl-CoA accumulation in heart. Our results show the "metabolic filtering" role of liver in maintaining efficient cardiac energy metabolism.

In order to understand the pathological mechanism of cardiac complication associated with PA, a PA-mediated cardiac complication model is essential. In year 2 of PAF award, we will first develop and confirm a mouse model with cardiac complication before pathological mechanism study. With the collaboration with Dr. Michael Barry, we will characterize cardiac function and metabolic phenotype of Pcca-/-(A138T) mouse that is a PA animal model created by Dr. Michael Barry. We will induce cardiac complication with Pcca-/-(A138T) mice by diets or stresses if it is necessary. After that, we will examine how cardiac energy metabolism is disturbed using stable isotope-based metabolic flux and RNA-Seq approaches. Furthermore, we will further investigate how propionylcarnitine expansion in the heart could deplete cardiac acetylcarnitine, acetyl-CoA buffer, and affects cardiac acute energy demanding. The long-term goal of our research is to find a therapeutic target on cardiac propionyl-CoA metabolism to mitigate cardiac complication associated with PA.

Free Testing Clinic for Amish PA Variant

The Community Health Clinic (CHC) of Topeka, IN will offer free genetic testing on specific dates for the Amish PA Variant (c.1606A>G) in the PCCB gene this fall which the PA Foundation has provided a grant to cover the expenses of the testing. The Amish PA variant can be missed on newborn screening, so the CHC and PAF have partnered up to help diagnose Amish community members at risk for significant PA complications. These free testing clinics will occur BY APPOINTMENT ONLY on October 27th, November 5th, November 10th, and November 12th from 3-8pm EST. Due to COVID-19 restrictions, you must make an appointment for testing for each individual person desiring testing. This free testing is on a first come, first serve basis and is available to any Amish community member or individual who is of Amish descent as testing is only for the specific Amish variant. Other PA-causing variants will not be detected in this testing. Please call The CHC at 260-593-0108 for more information or to schedule your free testing.

Vivienne's Story

My beautiful Vivienne was born on December 30, 2019. She weighed 8lbs.and 6 oz. We were all very happy with her arrival. Vivienne's sister was very happy and excited that she was finally going to be a big sister (big age gap difference 12 years). We noticed the day that she was born; she wasn't very interested in the bottle, they told us that it was normal, that many newborns are not interested in their bottle. We were discharged from the hospital and they told us to follow up with our pediatrician for Vivienne's check up. We followed up with our pediatrician and they told us that they were worried because Vivienne was losing weight very rapidly. They tested her for jaundice, and they checked her glucose levels in the office, and they all came back normal. They told us to come back the following day, so they could check her weight, again. They stated, if she loses weight again in one day, you need to take her immediately to the hospital; or, if you feel that something is not right then take her to the emergency room tonight.

I took Vivienne that night to the hospital. I knew in my heart something was not right. She was already vomiting frequently, lethargic, and not very responsive. They were running many blood tests on the baby. They pulled me to the side and told me that they thought that she had meningitis. They said that they were going to do a lumbar puncture (spinal tap) similar to an epidural. Next thing we know we are in the NICU! Once they transferred us to the NICU they said to us that my daughter had very high ammonia levels. They told us that nothing looked favorable for Vivienne and that most likely she was going to pass away. They asked, If we wanted to get a priest to give her holy sacraments. She was in need of a line for dialysis and that the first step was to take her to an anesthesiologist to put in a line, and they were not sure if she would even get past that point. She made it out and they transferred her to the PICU. That's when they told us that our daughter had Propionic Acidemia. They gave me a folder with all of the information. Vivienne had a team of doctors (neurology, kidney, cardiology, genetics, and pediatricians). She was on dialysis for a couple of days and thank God her ammonia levels went down and it was time to disconnect her from the dialysis machine. All of her teams signed off that it was okay to take her off the machine. Once they took her off the machine she didn't respond. She started bleeding internally, she started having pulmonary hemorrhage, they didn't know why. All the alarms from the hospital started ringing. All the doctors started coming into her room trying to revive her and intubate her, because now she couldn't breath on her own. As a parent seeing your child losing her life in front of your eyes it's extremely difficult; you feel impotent, useless, helpless. It was a traumatic experience to go through as parents; to see in front of your eyes that your daughter is losing her life. She goes back on dialysis and the medical team decided to put her enough blood product; so she wouldn't bleed out and coagulate (she ended up with a blood clot). She was sedated due to the intubation so she wouldn't feel pain. They say babies don't cry but I saw a tear out of her eye that day. They would tell us to go to the Ronald McDonald Charity house many times to rest; but, I couldn't leave my child. I was with her at all times. Then, a couple of days later she comes off the dialysis machine without any problems and the breathing tube was removed too; then, they said that she would need another operation. They said that they wanted to perform an operation for a g -tube. They said that could be a backup plan, if she ever didn't want to eat by mouth. At first, I didn't want to go forward with the operation and my husband did want to go start the process. Then we talked and decided to go forward with the g-tube operation and it was the one best decision that we took for her. The whole month of January 2020 she was hospitalized. When she was sent home we had to learn how to inject her Lovenox for her blood clot (it was one of the hardest things in my life to inject my baby twice a day), and give all of her medication and prepare her formula.

Then, in February, she was in the hospital again she had a metabolic crisis. In March, she was hospitalized again due to a metabolic crisis. By this time, I started to recognize the symptoms that would drive Vivienne to a metabolic crisis. She would spit up, vomit, not interested in her feed, very sleepy, lethargic, hiccups, gagging and dehydrated lips. By March, my husband and I had to organize ourselves. He would take our oldest daughter to school everyday and he would take care of things. I would stay with Vivienne in the hospital. Due to Covid-19 many things changed, it was difficult for us; hospital policies and visitation rules changed. Overall, Vivienne got tested for COVID-19, six times because that's the hospital's policy any time you get hospitalized you get tested (testing had to be done

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VIVIENNE'S STORY (CONTINUED FROM PG. 4)

to keep our hero's doctors, nurses, and staff safe). In April, again she was hospitalized due to a metabolic crisis. In May, she was in the hospital for three weeks for a metabolic crisis, and they also thought that she had another rare disorder called hirschsprung's. They decided to do a biopsy and she tested negative, and the whole month of June she was hospitalized until July 03,2020.

It's the first time in Vivienne's life that she has been out of the hospital for more than a month! It's been amazing! We have been going to genetics appointments weekly and then bi weekly. There have been formula changes every week, lab tests every week, but Vivienne has been home without any IV lines going bad and no daily lab work for ammonia levels, which is great! I am very thankful to God that Vivienne has been much better! Her dietician is amazing, very proactive, very attentive, and professional (dieticians are very important in our babies lives). The Propionic Acidemia Foundation web page has been very helpful! The prop nutrition management toolkit was very helpful! There's plenty of helpful and educational material on the foundations web page. I also wanted to thank Jill Chertow… She has been my support since the beginning of my journey! She has guided me and has always listened to me. I have cried and she has comforted me. I needed advice and she has provided it! She gave me courage to keep going in my hardest moments.

INTERVIEW WITH JOEL PARDO, NIH TRAINEE

Can you tell me about yourself and how you became interested in science?

I was always interested in the sciences. I think ultimately what propelled me towards a career in science was my research experience at the University of California, San Diego. The mentorship I received from Dr. Joshua Bloomekatz helped me develop the ability to reason scientifically and appreciate the opportunities to grow professionally. I learned from him how to design experiments to answer important scientific questions. We often had lengthy discussions about the direction of my project. He helped me make sense of the collection of observations coming from different sources and nurtured my own independent thinking.In gaining an appreciation for his analytical method of thinking, I began to see myself as someday contributing to scientific thinking as a physician-scientist.

During your training at NIH, you worked on a project to find new treatments using zebrafish. What did you find exciting and challenging about studying zebrafish?

Most people are familiar with mice, which are often used in science to find and test new drugs. Working with mice requires a lot of work to have enough animals needed for an experiment. Zebrafish, on the other hand, can produce hundreds of offspring after one breeding cycle. Zebrafish lay eggs directly into water, which also makes it easier to study them soon after they hatch. Somewhat surprisingly, the zebrafish enzymes that handle propionic acid are very similar to the enzymes in humans. These two properties of zebrafish make them an exciting model to study a disease like propionic acidemia.

One of the most challenging parts of my research in zebrafish was their size. Zebrafish offspring are very small, measuring less than a quarter of an inch. I had to spend a lot of time looking at zebrafish under the microscope and learn how to move them around without hurting them. This can be difficult as these small animals are fragile at this young age.

Can you tell us about your PA project?

Earlier in my work, we were able to get zebrafish, which had mutations in the genes linked to propionic acidemia. I needed to understand what propionic acidemia does to zebrafish. We were able to show that propionic acidemia in zebrafish looks a lot like the disease we see in patients. Fish with propionic acidemia had poor appetite, did not grow well, and had difficulty moving. Using special genetic tools, we then attempted to change how zebrafish processed propionic acid and helped them survive longer. Our preliminary results are proving promising, but more work is still needed.

What are your plans after you complete your training at NIH?

The NIH postbac program is a full-time research award for students that have recently completed a bachelor's degree and are considering a career in science or medicine. I was fortunate enough to join Dr. Charles Venditti's lab 2 years ago to work on the zebrafish project under Dr. Oleg Shchelochkov. I thoroughly enjoyed my post-bac experience. Looking back on the past 2 years, I feel the lab, and in particular the mentorship of Dr. Shchelochkov, has facilitated and nurtured my growth as a future physician-scientist with roots in propionic acidemia research. In 2019 I applied to MD/PhD programs at several US universities. After having traveled to over half a dozen states and interviewing at many fantastic universities, I ultimately decided upon the physician-scientist training program at University of Minnesota. As I plan my transition to the program, I am currently looking for winter coats.

PAF EVENT & FUNDRAISING SPOTLIGHT

UPCOMING/ONGOING EVENTS

- **September 26 - 15th Annual Tailgate Party & Corn Hole Tournament for PAF (1st Virtual!),** See GwenForACure.com for more info.
- **October 3 - Virtual Dance Party with Shayna**, 1:00 CDT. See below or email paf@pafoundation for more information.
- **October 24 - PA Virtual Meeting,** See pafoundation.com for updates
- **October 25 - Virtual Halloween Art with Shayna**, 4:00 CDT. See below or email paf@pafoundation for more information.
- **November 7 - Virtual Character Dance Party with Shayna**, 1:00 CST. See below or email paf@pafoundation for more information.
- **Novermber 15 - Virtual Thanksgiving Art with Shayna**, 4:00 CST. See below or email paf@pafoundation for more information.
- **December 1 - #GivingTuesday**

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: Julie Howard, Erika Gross' birthday. Thank you for making a difference.

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**: Trent McKinley
- **In Memory Of**: Nicholas Phillips
- **In Honor of Rare Disease Day**: The Villainettes made a donation of $1330 in honor of Diego Cardona

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.

FALL FUN TIME WITH SHAYNA

Hi everyone! My name is Shayna Rosenson and I am currently a senior at the University of Wisconsin-Madison studying finance and disability rights & services. On a more personal level, I am the cousin of Jordan Franks and the niece of Jill Chertow. I first began my involvement with the Propionic Acidemia Foundation in 2016 when I worked with Jill to nominate PAF for Deerfield High School's annual fundraising beneficiary. I am excited to share that I am back this fall to lead some fun fall activities for the whole family over Zoom! If you are interested in participating in any of the activities, please email paf@pafoundation.com for the zoom links and more information. I look forward to seeing many of you soon!

Saturday, October 3rd at 1:00 CDT: **Dance Party**

Sunday, October 25th at 4:00 CDT: **Halloween Art**

Saturday, November 7th at 1:00 CST: **Character Dance Party**

Sunday, November 15th at 4:00 CST: **Thanksgiving Art**

Propionic Acidemia Foundation Annual Report FY 2019-2020

FINANCIAL REPORT

Revenue:	
Contributions	$85,564
Interest	$10,997
Program Revenue	$1,100
Total Revenue	$97,661
Expenses:	
Program Service	$84,370
Management & General	$1,959
Fundraising	$2,687
Total Expenses	$89,016
Cash Assets 8/01/2019	$459,731
Cash Assets 7/31/2020	$468,376

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 $525

Thank you for your donations and kind notes 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, 2021.

PROGRAM ACCOMPLISHMENTS

- Awarded new research grant to Ken Maclean, PhD, University of Colorado Denver, " Chemical Chaperone Treatment to Restore Enzyme Activity in Folding Mutations of Propionyl-Co-A Carboxylase: Towards a Personalized Therapeutic Strategy in Propionic Acidemia (PA)
- Awarded new research grant to Rajavel Elango, PhD, The University of British Columbia, Canada Optimizing amino acids in medical foods to manage propionic acidemia
- Awarded continuation 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.
- Awarded a No cost grant extension to Guofang Zhang, PhD, Duke University, Propionyl-CoA and propionylcarnitine mediate cardiac complications in patients with propionic acidemia
- 114 Participants in PA Patient Registry
- Distributed fall and spring newsletters to affected families,

Warriors Birthday Club

This year birthday cards will be made by students at Oak Lawn-Hometown Middle School and St. Linus 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.

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.*

Searching for a Cure
Hope for Our Children

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Propionic Acidemia Foundation

PAF volunteers and board members are needed!

Join and follow Propionic Acidemia Foundation on Face-