SEARCHING FOR A CURE HOPE FOR OUR CHILDREN

Propionic Acidemia Foundation

VOLUME 1, ISSUE 30 SPRING 2021

Thank you for your support, fundraisers, generous donations and kind notes throughout the past year. Your support overwhelms us and continues to be a source of inspiration. Your efforts have allowed PAF to fund an additional two new research grants (see page 2). The valuable research that is funded would not be possible without your support. Please continue to spread awareness and share your story. We would love to hear from you and encourage you to consider volunteering.

PAF Upcoming Virtual Events

Saturday, April 10, 2021, 11:00 AM Eastern

PAF and OAA invite you to Advancing mRNA to Treat Organic Acidemias Webinar
(see page 9)

Saturday, April 17, 2021, 1:00-2:30 PM Eastern

PAF and OAA invite you to New Horizons for MMA and PA Webinar
(see page 11)

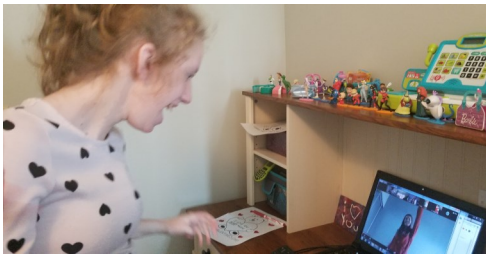
Sunday, April 25, 2021, 2:00 PM Eastern

PAF Fun Time Dance Party with Shayna - Fun for all ages!

Saturday, May 1, 2021, 2:00 PM Eastern

PA Chat - An opportunity to share your story and provide advice for new families

Registration is free at www.pafoundation.com



PA Registry

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

As of March 1, 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.

NEW RESEARCH GRANTS AWARDED

PAF Awards $49,953 New Research Grant

"Aberrant protein propionylation and distinct histone marks in propionic acidemia: new disease mechanisms and risk factors for cardiac disease"

PI: Pawel Swietach, Professor of Physiology, Department of Physiology, Anatomy & Genetics, University of Oxford, England

The challenge placed on our hearts – to contract and relax in a correct sequence and with adequate strength – is formidable. The elegant biological solution to this mechanical problem is an organ that pumps millions of liters of blood to support life for many decades. However, the quality and span of a person's life is strongly linked to cardiac health. Thanks to scientific breakthroughs, better treatments are now available for cardiac disease, allowing patients to live longer and happier lives. Our goal at Oxford University's British Heart Foundation Centre of Research Excellence is to ensure that scientific progress addresses a wide spectrum of disorders, irrespective of their incidence.

Cardiac problems are common in propionic acidemia (PA). Sadly, dilated cardiomyopathy and long-QT syndrome are often the cause of childhood death. In order to treat and prevent these cardiac problems, we must first understand the underlying mechanisms. Once these processes are described, our aim is to identify targets for drugs or interventions. We believe that this ambition is achievable thanks to the wealth of knowledge about the heart and the vast repertoire of drugs approved for therapy in various other cardiac conditions. Many of these drugs could be "repurposed" for PA-associated disorders, giving hope to many families for a timely treatment.

For this PAF-funded project, we have assembled a consortium of scientists who are eager to devote their expertise to studying PA. My laboratory's expertise is in cardiac cellular physiology in the context of acid-base disorders. We are joined by Tom Milne who is Associate Professor in Epigenetics at Oxford, Holger Kramer, an expert on proteomics, and Steve Krywawych, principal biochemist at Great Ormond Street Hospital in London. Resources and facilities made available to this project include a mouse model of PA, courtesy of Michael Barry and Lourdes Desviat, methods to characterise cardiac function from the cell to organ level, as well as measurements of changes at the protein and gene level. This interdisciplinary but focused approach allows us to identify potential targets for PA treatment. Indeed, our preliminary findings point to one such enzyme, and the aim of this project is to test and validate our hypothesis.

PA is associated with major metabolic changes, and many of these substances are not merely intermediates in a chain of events, but can have strong biological actions that are not always intuitive to predict. Our project will investigate how the build-up of propionate affects cardiac genes through a chemical reaction that causes DNA scaffolds (called histones) to "open up" genes that should not normally be expressed in a healthy heart. Many genes will be affected by this, but some are more closely linked to the cardiac disorder. After identifying these lead genes, we will test the extent to which blocking these could be curative. In parallel, we will investigate if propionate can also react with other targets in the cell, such as proteins underpinning contraction. Indeed, our work suggests that a promising avenue for research relates to so-called excitation-contraction coupling, a process that converts cardiac electricity to a mechanical response.

We are excited to be part of the PA research family and wish to take this opportunity to invite patients, carers, and supporters to our lab for a visit.

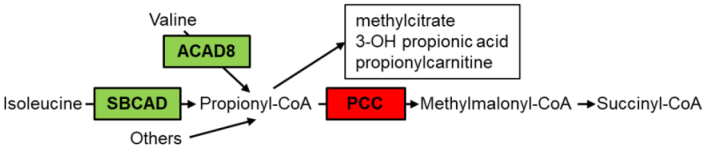
PAF Awards $50,000 New Research Grant

"Substrate reduction as a novel therapeutic strategy for propionic acidemia"

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

Amino acid metabolism and in particular the degradation of valine and isoleucine are a significant source of propionyl-CoA, the substrate of propionyl-CoA carboxylase. Current treatment of propionic acidemia aims to decrease the degradation of valine and isoleucine through medical diets and avoidance of fasting. Drs. Houten and DeVita, the investigators on this project, aim to develop a pharmacological substrate reduction therapy for propionic acidemia that limits the degradation of these amino acids. They 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 investigators anticipate to find a few hit 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.



EFFECTS OF PROPIONIC ACIDEMIA IN BRAIN

Maria L Cotrina, PhD
NYU Grossman School of Medicine, New York, NY 10021

Propionic Acidemia (PA) causes the accumulation of propionic acid (PPA), its toxic derivatives, and ammonia in the body. The disease affects every organ and has particularly severe manifestations in the brain. Children with PA frequently experience seizures, cognitive and language impairments, and optic-nerve atrophy. But despite the severe effects of the disease on the brain, little is known about how PA affects the nervous system. Two recent studies have tried to shed some light on this important question.

The first study involved the PA registry, which was created and maintained by PAF. As you may know, the registry has been collecting data reported by PA patients and their families since 2012. The new study found that children with PA are diagnosed with Autism Spectrum Disorders (ASD) at a higher frequency than the general population (21% compared to 1.7%) and confirms some earlier reports on the frequency of ASD in PA children.

What this means is that a diagnosis of PA is a risk factor to develop ASD. Although this may come as a surprise to the PA community, we know that this increased risk of an ASD diagnosis has also been observed in patients with other syndromes caused by mutations in a single gene, such as Fragile-X-syndrome, Rett syndrome or Duchenne muscular dystrophy.

The study also found that the age of diagnosis of ASD in PA children is greater than the age reported in the national data for the general population. In this case, children tend to be diagnosed when they are older. Also, the study showed that PA patients diagnosed with ASD often have intellectual impairment, independently of the presence of stroke or basal-ganglia damage. Last, the study reported that both boys and girls with PA are diagnosed at the same rate with ASD. This is an important difference with the known prevalence of ASD diagnoses in the general population, which tend to affect more boys than girls (about 4 boys are diagnosed with ASD per every girl with the same diagnosis).

These results raise the possibility that, in PA children, the prolonged exposure to high levels of propionic acid in brain may be more relevant for an ASD diagnosis than having an acute crisis once or twice in their life.

The second study, which just appeared last month, tried to understand some of the mechanisms by which PA affects the brain, focusing on a particular type of brain cells called astrocytes. Astrocytes are very important to maintain a healthy brain because they help clean up some of the waste created by brain activity. In fact, they are the main cell type with the capacity to eliminate the high ammonia levels that accumulate in brain of PA patients.

What this study found is that astrocytes from mice with a defective PA gene did not show any signs of damage or sickness. What is more, these mice did not show any significant changes in brain development or brain-cell loss. However, a low level of inflammation was present across all brain areas analyzed in this study.

As surprising as this may seem, it is very possible that there were no signs of damage in the brain of these mice because they do not replicate PA well enough in the nervous system to see such damage. For example, although these mice show signs of heart problems, which are common in PA patients, none of the mice showed brain strokes, which are often suffered by PA patients.

In summary, these two studies represent some early steps to tackle the complex question of why PA affects the brain so severely. It is important to highlight that better animal models are needed to make sure that researchers can mimic the disease adequately in the lab. The availability of these models is critical if we want to be able to test potential therapeutics to improve brain function in our children with PA.

Additional reading:

- ML Cotrina et al., Impact of propionic acidemia in brain astroyctes. BioRxiv 2021.
doi: https://doi.org/10.1101/2021.02.07.428966
- M. L. Cotrina, et al. High prevalence of self-reported autism spectrum disorder in the propionic acidemia registry. JIMD reports 2019: 1-6.

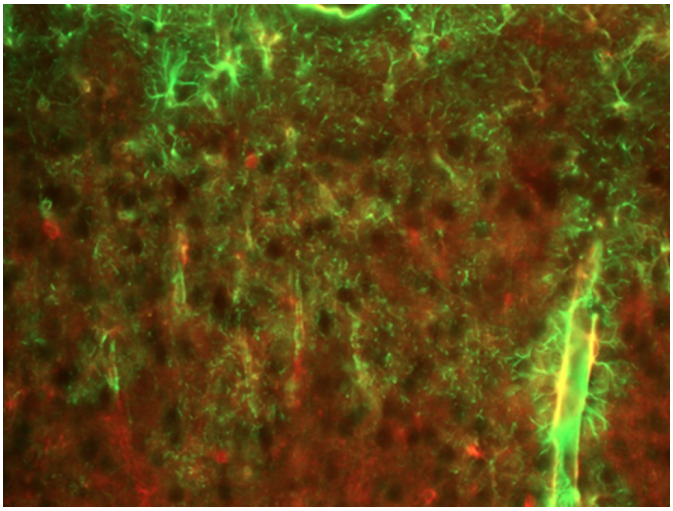


Figure 1. High ammonium activates astrocytes. Astrocytes surrounding blood vessels in the brain light up (green) when there is high ammonia in the blood.

RARE DISEASE DAY SPOTLIGHT

VIVIENNE: I would like to thank two amazing human beings that have helped Vivienne along her journey with Propionic Acidemia. First, I would like to thank Ms. Heather, who is Vivienne's Nutritionist/Dietician. Since she took on Vivienne's case, Vivi's health has improved. She has made such a difference in Vivienne's life! Now, I know why so many parents emphasized the importance of a great dietician! Ms. Heather has been very caring, very attentive,a great listener and very committed to Vivi's case!

Second, I would like to thank Dr. Baker! Dr. Baker has been an extraordinary geneticist! His dedication and amazing care has helped Vivi stay away from many hospital stays. I feel so blessed in having both Dr. Baker and Ms.Heather as Vivienne's care team. They both have gained my confidence. Dr. Baker and Heather truly made a difference in Vivienne's life! Thank you from the Lopez Family!

NALANI: Nalani has been lucky to have some amazing people in her life helping her along in her journey. She has been attending a weekly social group at Coeur Academy in Missouri for about 6 years now. They get together, talk about their week, plan activities and play games. They cook a "Thanksgiving feast" and exchange gifts on Christmas. They go shopping and go out to eat together. She is the only girl and tells everyone she meets that she has 4 boyfriends. Nalani is extremely social and this program has given her a group of true friends. I am so thankful to them. I don't know what she would do without Ann, Sarah and her boyfriends at social group! - Angela

IN MEMORY OF RAYYAN

Rayyan born 21 May 2000.

He was diagnosed by birth at King Faisal Hospital Riyadh, Saudi Arabia. Despite several hospital visits he was growing normal. Eating and drinking by mouth. He loved painting and creative work. He wanted to do a job and earn for his family. He loved to play games on PlayStation and XBox. He had long QT interval, and was on dopamine for some years. He was on L-carnitine, Biotin and milk formula Prophree, Propimex. He was an inspiration for this world. Every Friday he distributed sweets among children in his school. He made coffee for his favourite teacher every morning when going to school.

Two years passed after 16 years of age he did not need any hospital admission. Doctors allowed him to take 53g protein daily by mouth. Suddenly one day vomiting started and he was lethargic a lot. Admitted to Children's hospital in Pakistan, Lahore. His plasma ammonia (100) and lactate (50) went high. Platelets went down to 65. Doctors thought it was some infection, so they started him on IV antibiotics and fluids for dehydration. His constipation was resolved by doctors. But on the 5th day of admission he went into a coma and ventilator. Blood ph dropped and acidosis increased. He was started on sodium bicarbonate. And sodium benzoate. L-carnitine through IV But he could not go through it and passed away on 31st January 2021.

We will never forget him. He was a star for this world. We will bear this loss through our whole lives. His three sisters, mom and dad will miss him forever.

Our love to RAYAN (18years 9 months) and brother AOUN (16 years) who passed away.

Moderna

Advancing mRNA Medicines to Fight and Prevent Disease

Moderna is driven by our mission to deliver on the promise of mRNA science to create a new generation of transformative medicines for patients. We are currently advancing mRNA clinical studies on our development candidates to address serious unmet needs across several therapeutic areas and multiple diseases, including Propionic Acidemia (PA), Methylmalonic Acidemia (MMA) and other rare genetic diseases that are caused by defects or deficits in proteins expressed by liver cells.

Moderna is taking a different approach to address the underlying cause of these diseases by delivering mRNA therapeutics intravenously (IV) to potentially stimulate production of therapeutic proteins in the liver in ways that cannot be achieved with other technologies. Our approach aims to help the body make its own missing or defective protein (in this case, PCC). mRNA technology does not change the genetic information of the cell, and it is short-acting. It acts like traditional drugs that can be adjusted over time based on the dose and frequency needed. In simple terms, we are working to provide physicians and patients with a "controllable" way to start and manage their therapy over time.

As we continue our work at Moderna to advance the development of mRNA-based therapeutics, we are pleased to share that our first program in PA, the Paramount Study, is now enrolling study participants in the United States.

People who are diagnosed with PA are missing the propionyl-CoA carboxylase (PCC) enzyme, which is responsible for the breakdown of certain proteins and fat. When this enzyme is missing, it is difficult for cells in the body to turn food into energy, leading to toxins building up in the bloodstream. Currently, PA is treated by lowering the amount of protein eaten daily, taking dietary supplements or antibiotics, or getting a liver transplant.

moderna | paramount study

The Paramount Study is a Phase 1/2 study. It is designed to evaluate if an investigational treatment called mRNA-3927 is safe and effective in reducing the symptoms of PA in individuals one year of age and older. mRNA 3927 is an investigational intravenous (IV) infusion treatment that instructs a persons' body to make a PCC enzyme that works.

More information including full trial inclusion and exclusion criteria can be found at https://trials.modernatx.com or by visiting https://clinicaltrials.gov

"As a company, we often talk about the societal responsibility we feel to deliver on the promise of mRNA science for patients. That sense of responsibility is felt with great intensity, and urgency, by the Rare Diseases team. We understand that, for so many patients suffering with a debilitating rare disease, there are no approved treatments. We are committed to leveraging our mRNA platform to advance medicines for some of these diseases and bring new hope to patients and their families."

- Paolo Martini, Chief Scientific Officer, Rare Disease

PAF Event & Fundraising Spotlight

UPCOMING/ONGOING EVENTS

- **Fall 2021 - 16th Annual Tailgate Party & Corn Hole Tournament for PAF (Maybe Virtual),** Visit GwenForACure.com for more info.

PAST EVENTS

- **15th Annual Tailgate Party & Corn Hole Tournament for PAF (1st Virtual!)** - raised $11,573
- **PAF Virtual Family Day** - We are grateful for our speakers Dr. Benjamin Goodlett, Dr. Oleg Shchelochkov, and Dr. Charles Venditti and for all that attended. Due to the wonders of technology we were able to reach more than double the number of families that could previously attend in person. The videos are available on the PAF website.

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: Tahirah Anderson, Debbi Buck, Maria Cotrina, Giuseppe DiMaggio, Jill Chertow, Erika Gross, Jaime Lyn's, John Moss, Rachel Mullins, Sarah Mullins, Andrea Sherwin, Shayna Rosenson, Cara Popowicz Harmon, Brayden Murphy, Lisa Napiwocki, Angela Waits, Cassie Sirett, Brittany Smith, John Moss, Veronica Lopez, Kathleen Rusch, Michael Woolery

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**: Nila Branch, Kaitlyn Burns, Nicholas and Zachary DiMaggio, Allison Ellis, Lucy Harding, Dylan Jaehnke, Reuben Kleckley, Reily and Judson Lenert, Kate Lowry, Joas and Elijah Lehman, Laura Lemire, Leah Masten, Trent McKinley, Zach Matz, Michael Messersmith, Gabrielle Millett, Gwen Mouat, Brandon Napiwocki, Carolyn Schlein, Emmy Sherwin, Ben Sweetman, Kayleen Marie Trejo, Isabella Velazquez, Sharlene Weaver, Annette Weaver, Chase Workman, Brett Young
- **In Memory Of**: Courtney Leigh Callahan, Sean Patrick Callahan, Alexa Faith Cardone, Kerrie Fessler, Jordan Franks, Vincent Phlip Franze, Connor McKillop,Nicholas Phillips, Abraham and Amanda Sleiman, Talli Smith, Angelica Stageman, Kirstyn Tripp, Keith Weaver

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.

HemoShear Therapeutics PAF Benefit in February

The team at HemoShear Therapeutics raised money for PAF in celebration of Rare Disease Day by donating a dollar for every mile the staff spent walking/biking/running in February. They donated $5,000 to support our work!

HemoShear is developing HST5040, an oral therapy designed to correct metabolic abnormalities associated with MMA and PA. HST5040 has the potential to be active throughout the body, including the brain, heart, liver, kidneys and muscles. The drug can be taken conveniently at home as a daily liquid formulation by mouth or through a gastric feeding tube.

The company is sponsoring the **HERO** (**HE**lp **R**educe **O**rganic Acids) clinical study (See page 11). The HERO Study is enrolling at least 12 patients with MMA and PA aged 2 and older at select leading children's hospitals in the United States.

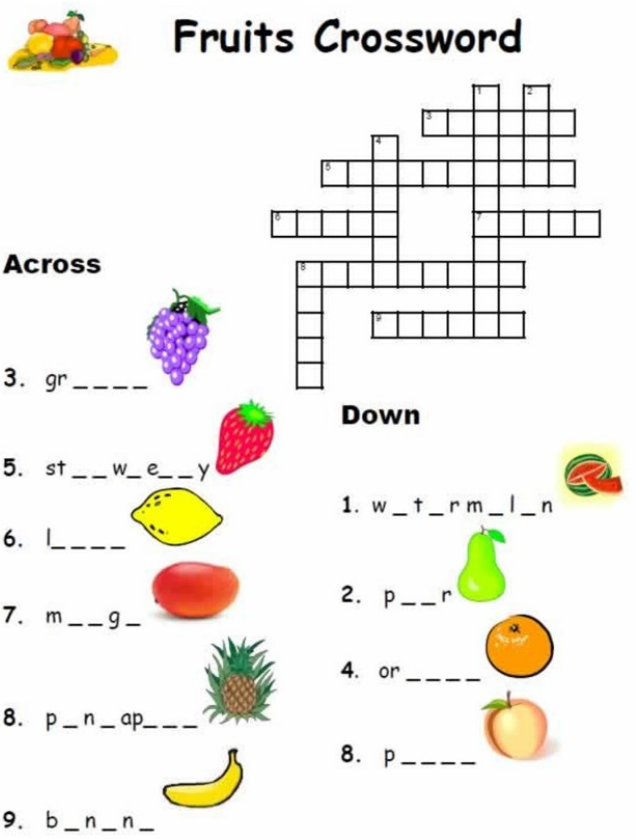
Study sites are opening now. You can learn more about the study and locations on Clinicaltrials.gov.

Kids' Corner

Shayna Rosenson started running zoom events in the fall and has continued into the Winter and Spring. It is fun for all ages. We are excited to share that Shayna will back this spring and summer to lead some fun activities for the whole family over Zoom!

Sunday, April 25th, 2:00 pm Eastern

If you are interested in participating in any of the activities, please email paf@pafoundation.com for the zoom links and more information. We look forward to seeing many of you soon!



Warriors Birthday Club

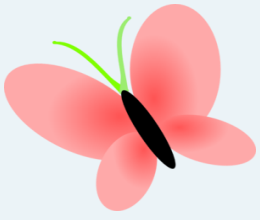
This year birthday cards will be made by students at Oak Lawn-Hometown Middle School and St. Linus for participating families. We are thankful they have volunteered to do it again this school year. Please sign up a patient or sibling for the Warriors Birthday Club at http://www.pafoundation.com/warriors-birthday-club/.

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

We want to hear from you!

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

Fall newsletter submissions due by August 1, 2021.



PAF REQUEST FOR PROPOSALS

Submission Deadline: October 1, 2021
Awards announcement: January 15, 2022
Funding begins: Upon execution of grant agreement

Primary Research Mission

PAF is a non-profit organization whose primary mission is to help advance research devoted to find treatments and a cure for propionic acidemia. By funding research, we aim to accelerate new knowledge, discovery, development and/or evaluation of therapeutics leading to better treatment and a cure for all individuals affected by PA.

Application categories:

1) Research Projects – Basic and Clinical research including initial grant request or continuation grant supporting projects designed to understand the molecular basis of the PA pathology and explore possible therapeutic avenues for the treatment of this condition. Past awards have ranged from $3,000-50,000 per year and may last 1 or 2 years upon competitive renewal.

2) Post-Doctoral Fellows Program

This program provides financial support up to $50,000 per one year for a metabolic/genetic fellow working on a research project in PA. This salary is intended to supplement any existing institutional support

PAF is particularly, but not exclusively, interested in the following areas of research:

- Development of chelating compounds for PA toxicity
- Risk factors for development of brain damage, pancreatitis, kidney disease, cardiomyopathy and/or arrhythmias,
- Disease modifiers in PA
- Development of new animal or cell/tissue-models for the study of PA
- Improved treatment including nutrition

Grants will be evaluated by the PAF Medical Advisory Board and Board of Directors based on the scientific validity and merit of the proposed research; technical feasibility; impact on accelerating discovery, development or evaluation of therapeutics; potential translation to humans; innovation; and ability to complete the research within the funding period.

Additional evaluation criteria include the relevance of the proposed research to PAF goals, specific research priorities and how the project fits with the current project portfolio.

If you have any additional questions regarding applications and funding regulations, please email research@pafoundation.com.

APPLICATION GUIDELINES

Applicants are invited to submit a full proposal (single-spaced with 0.5" margins using no less than 11 point Arial fonts). Full proposals should include the following in order and be submitted in one electronic document in the order listed below to research@pafoundation.com

- Project Title
- Principal Investigator Name, title, address (institution), phone, and email
- PAF Grant Type: initial research grant, a continuation grant, or a Fellowship
- Abstract/Summary of the Project (1 technical and 1 for the lay audience)
- Introduction
- Hypothesis to be tested
- Significance of proposed research to individuals with PA
- Specific Aims/Objectives

PAF REQUEST FOR PROPOSALS (CONTINUED)

- Preliminary Studies if applicable
- Methods and procedures
- Proposed results and potential challenges
- Project timeline
- Detailed Project Budget of total direct cost estimate for all categories of requested support including justification in U.S. dollars. *Indirect costs will not be payable through the grant.* Include total proposed by year if project period if longer than 1 year in scope.
- Biosketch for all key scientific and technical personnel. The NIH or other standard biosketch format is acceptable.
- Relevant Publications during the past five-year period. For continuation applications, list research articles submitted during the current grant period (published or in press).
- Assurances and Collaborative Agreements including Letters of Intent to Collaborate and Letters of Agreement from consultants
- Other Sources of Support including current and pending research support of all key scientific and technical personnel. Identify other support for the proposed project(s) including title, abstract, annual and total amount of the grant, inclusive funding period and percent of effort of the applicant. If there are no other grants, indicate "none."

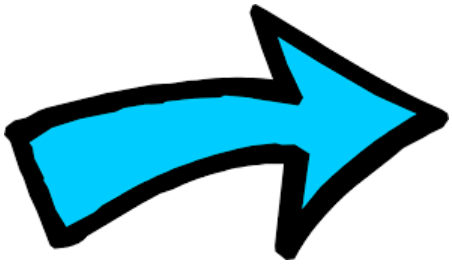
Number of awards each cycle is dependent on the number of applications, outcome of review and the availability of funds. PAF is not obligated to make awards following each grant cycle.

Applicants without a faculty appointment (e.g., post-doctoral level) must also submit a letter of support from their project mentor.

Please contact PAF with any questions at research@pafoundation.com or 877-720-2192

Register for the Zoom webinar!

http://www.pafoundation.com/events/



CARBAGLU® APPROVAL UPDATE

CARBAGLU® (carglumic acid) Tablets for Oral Suspension 200mg is Now FDA-Approved to Treat Acute Hyperammonemia Associated with Propionic Acidemia and Methylmalonic Acidemia

Recordati Rare Diseases has received FDA approval for CARBAGLU® (carglumic acid) to supplement standard of care treatment for acute high blood ammonia levels due to propionic acidemia (PA) or methylmalonic acidemia (MMA) in pediatric and adult patients. CARBAGLU is the first and only product with this indication.

PA and MMA can lead to the buildup of various toxins in the blood that can impair the urea cycle, an important pathway in the metabolism of protein. The urea cycle helps remove excess ammonia, which is a product of protein breakdown. If the urea cycle does not work properly, ammonia levels can increase in the blood. PA or MMA patients may develop high ammonia levels, hyperammonemia, during an acute metabolic crisis.

CARBAGLU is a medication that is structurally similar to N-acetylglutamate (NAG), a compound required by the body to start the urea cycle. The toxic substances that build up due to PA and MMA may lead to less NAG production. CARBAGLU acts as a replacement for NAG to help activate the urea cycle, which may lower high ammonia levels.

In a randomized, double blind, placebo-controlled, multi-center study of PA and MMA patients with acute high blood ammonia levels, patients received either standard treatment and CARBAGLU or standard treatment and a placebo. The study observed that high ammonia levels were reduced more quickly in patients treated with CARBAGLU compared to patients treated with a placebo over a 7-day period.

Indications and Usage

Carbaglu® (carglumic acid) tablets for oral suspension 200mg is a prescription drug used in all ages to help treat the following:

CARBAGLU is used to supplement standard of care treatment for acute high blood ammonia levels due to propionic acidemia (PA) or methylmalonic acidemia (MMA).

Important Safety Information

Contraindications: None.

Most common side effects in ≥5% of patients are: lower than normal white blood cells, reduced red cells in the blood, vomiting, abnormal levels of minerals in the body, decreased appetite, low blood sugar levels, lack of energy/ unresponsiveness, brain disease that alters brain structure or function, and inflammation of the pancreas/ increase in a type of protein made by the pancreas that helps the body digest fats.

To report SUSPECTED side effects, contact Recordati Rare Diseases Inc. at 1-888-575-8344 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

To read the recently revised Full Prescribing Information, including Instructions for Use, visit www.carbaglu.com. The new Pl includes important updates for treating hyperammonemia for all labeled indications.

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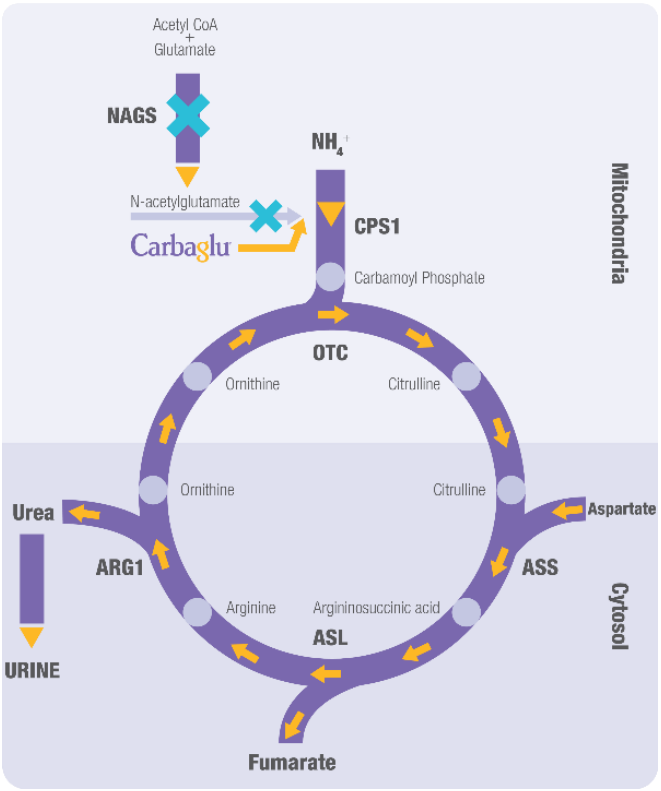

Publication Note: The PAF Newsletter *is published twice a year. Readers may subscribe by writing to PAF, registering online or calling 877-720-2192. Letters and article submissions are welcome for consideration and may be sent to paf@pafoundation.com or mailed to Propionic Acidemia Foundation 1963 McCraren, Highland Park, IL 60035. If you would like to be removed from our mailing list or receive the newsletter via email, please contact us.*

HEMOSHEAR THERAPEUTICS

Dear MMA and PA Community,

We are excited to inform you that our **HERO** (**H**Elp **R**educe **O**rganic **A**cids) clinical study has begun.

The HERO Study is enrolling at least 12 patients with MMA and PA aged 2 and older at select leading children's hospitals in the United States.

HELP REDUCE ORGANIC ACIDS HERO STUDY

The study is currently open at the University of Minnesota in Minneapolis, MN and Children's Mercy Hospital in Kansas City, MO. More sites will open soon and you can learn more about the study and locations on Clinicaltrials.gov.

The HERO study will assess HST5040, an oral therapy developed by HemoShear to 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 drug can be taken conveniently at home as a daily liquid formulation by mouth or through a gastric feeding tube.

ATTEND WEBINAR

REGISTER NOW!

HemoShear is collaborating with OAA and PAF to conduct a webinar, New Horizons for MMA and PA on Saturday Apirl 17, 2021 from 1 pm – 2:30 pm Eastern.

This webinar will feature a panel of experts to educate families about the current state of treatment and potential future options. The speakers will talk about how the clinical research process works and share information about HST5040 and the design of the HERO Study.

YOU ARE A HERO!

Making medical progress to improve the quality of life for MMA and PA patients is going to be a collaborative process between industry, clinical researchers and families. We invite you to visit our website and sign up if you want to receive updates from us.

We are humbled and excited to see if our drug can make a positive difference in patients' lives.

On behalf of the entire HemoShear team, thank you for your interest and support.

Sincerely,

Brian Wamhoff, PhD
Co-Founder and Head of Innovation

Searching for a Cure
Hope for Our Children

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