SEARCHING FOR A CURE HOPE FOR OUR CHILDREN

Propionic Acidemia Foundation

VOLUME 1, ISSUE 17 FALL 2014

Flu season guide For patients with Inborn Errors of Metabolism

What is seasonal flu? Seasonal influenza or "the flu," is caused by influenza viruses, which infect the nose, throat, lungs. In contrast to other viral respiratory infections, such as the common cold caused by rhinovirus, the flu can result in severe illness with life---threatening complications. Complications that can occur with flu include pneumonia, bronchitis, sinus and ear infections.

When is flu season? Flu viruses circulate throughout the population all throughout the year. An increase above baseline flu activity occurs in the United States during the Fall and Winter and is known commonly as the "flu season". Flu activity usually peaks in January or February, but it can occur as early as October and as late as May.

What are the symptoms of flu?

• Fever or chills • Cough • Sore throat • Runny/stuffy nose
• Muscle/body aches • Headaches • Tiredness

How does flu spread? People with flu can infect others up to 6 feet away. Flu viruses are spread mainly by droplets made when people with flu cough, sneeze or talk. These droplets land in the mouths or oses of people who are nearby. A person might also get flu by touching a surface or object that has flu virus on it followed by touching their mouth or nose. Healthy adults are infectious beginning 1 day before symptoms develop and up to 5 to 7 days after becoming sick. Children may pass the virus for more than 7 days. Symptoms start 1 to 4 days after the virus enters the body.

Tips for flu prevention in patients with IEM:

1) Get vaccinated. This includes not only IEM patients but family members as well. Seasonal flu vaccination is available as early as September for a given flu season.
2) Avoid contact with sick people. Sick individuals should avoid contact with other for at least 24 hours after the fever has gone.
3) Cover your mouth with a tissue when you cough or sneeze. Younger children can cough or sneeze into their elbow. (continued on page 2)

"Biomarkers for Neurological Injury in PA"

Seeking cooperative children and adults for *MRI study in Washington DC* to see impact of PA on brain markers. Subjects must be able to travel to DC and be stable and do MRI without sedation.

Travel costs and incentive paid. Study takes one day and involves advanced MRI and cognitive testing. Contact Ileana Pacheco ip126@Georgetown.edu or Dr Gropman at agropman@CNMC.org.

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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.

NIH MINI STUDY/FLU VACCINES FAQ (CONTINUED FROM COVER)

4) Prevent the spread of germs. Avoid touching your eyes, nose and mouth.
5) Wash your hands with soap and water or a hand sanitizer.
6) Clean and disinfect surfaces and objects that may be contaminated by flu or other germs. **(cont. pg. 5)**

Why should individuals with IEM get vaccinated this season? In addition to the complications mentioned above that are associated with flu (e.g. pneumonia), patients with IEM have an additional concern. Many patients with IEM, including organic acidemias, fatty acid oxidation defects, urea cycle disorders and mitochondrial disease may experience an acute deterioration in their metabolic status during an infectious illness. This "acute decompensation" is due in part to the catabolic stress associated with illness. With fever, caloric needs are greatly increased. At times, these caloric needs may not be met due to decreased food/fluid intake, nausea and vomiting. To keep up with this increased need for calories during infection, body fuels including carbohydrate, fat and protein are utilized. For patients with IEM, this may lead to the build up of toxic metabolites or energy failure due to their underlying enzyme deficiency.

How do flu vaccines work? Each year, Public Health Professionals need to predict which flu strains will be prominent in the coming flu season. These strains then form the basis for that season's flu shot. The flu shot is an inactivated vaccine (containing killed virus) based on these predictions. For patients with IEM, the vaccine is given via a needle in the arm. This vaccination causes the immune system to produce protective antibodies against the flu strains contained in the vaccination. It takes 2 weeks to develop these protective antibodies. It should be noted, however, that the flu shot does not protect against other respiratory viruses such as the common cold caused by rhinovirus.

Why do patients with IEM need to get vaccinated for flu every year? A flu shot is needed every year due to the fact that flu viruses are constantly changing. New flu viruses may appear each year. The flu vaccine is formulated each year to keep up with these changing flu viruses.

When is flu vaccine available? The CDC advises that people get vaccinated against influenza as soon as the vaccine becomes available. Influenza seasons can be unpredictable, and can even start as early as October. At the NIH Clinical Center, flu shots are available via the NIH MINI Study (see below), beginning in September.

How effective is the flu vaccine? In general, studies have supported that flu vaccination benefits public health, especially when the flu vaccine matches circulating flu viruses.

Do vaccines offer protection in patients with IEM? This is really an unanswered question. Since infections can trigger life---threatening acute metabolic crises in children and adults with IEM, we have decided to characterize the function of the immune system in patients with IEM. The standard of care for IEM patients is routine vaccination for influenza. However, there have been no studies to investigate whether the response to vaccination is normal in IEM patients. Vaccination represents a challenge to the immune system and can tell us how well it may be functioning. IEM patients may have enzyme deficiencies in their immune cells, a build--up of toxic metabolites, nutritional deficiencies, and energy deficiencies, all of which may impact immune system function.

The NIH MINI Study: Metabolism Infection and Immunity in Inborn Errors of Metabolism (www.genome.gov/mini) is an exciting study at the NIH Clinical Center (clinicalcenter.nih.gov). The main goal of our study is to learn about the function of the immune system in metabolic disorders. To learn whether you or your child develops immune protection to the flu vaccine or to learn more about your/your child's immune function, please contact us below.

For more information about the study please visit our Web site: http://www.genome.gov/MINI or contact the study coordinator, Janet Shiffer, C-RNP by phone at (301) 451-9145 or by email at ministudy@mail.nih.gov.

PAF awards Dr. Jan Kraus at University of Colorado Denver a no cost extension for his grant titled "Enzyme Replacement Therapy for Propionic Acidemia" for $13,433. This grant extension is through 12/31/2015.

UPDATE: GENE THERAPY RESEARCH, THE BARRY LAB, MAYO CLINIC

Adam J Guenzel and Michael A Barry

Background

Gene therapy research in the Barry Lab at Mayo Clinic has been supported with funding from the Organic Acidemia Association, the Propionic Acidemia Foundation, as well as by the Mayo Clinic Center for Regenerative Medicine. Our work has focused on developing a mouse model of propionic acidemia (PA) that can be used for basic study of PA disease and development of gene therapy vectors for treatment of PA. The original mouse model generated by Dr. Miyazaki at UT-Southwestern lacked both copies of the *PCCA* gene that encodes one subunit of the propionyl-CoA carboxylase (PCC) enzyme. This lack of PCC meant that the mice only survived 36 hours making analysis of disease processes or testing of therapies difficult.

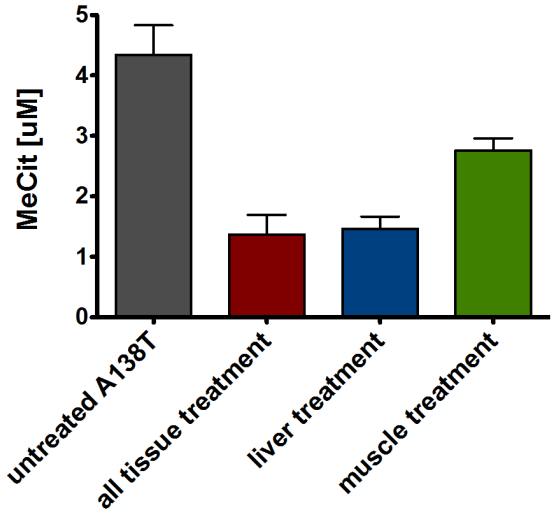


Figure 1. Methylcitrate correction after tissue-specific treatment. Methylcitrate levels were measured in the blood 45 weeks after injection with AAV vectors capable of expressing PCCA protein in all treated tissues, or specifically in the liver or cardiac and skeletal muscle.

To create a more compatible model, we introduced a human gene encoding PCCA that had an A138T mutation that was identified in a patient with propionic acidemia by Dr. Ugarte's lab at Universidad Autònoma de Madrid. In collaboration with Dr. Jan Kraus at the University of Colorado, we determined that the A138T mice have approximately 2% of normal PCC enzyme activity in their livers. Unlike the original PCCA mice with no PCC activity, most of these A138T mice survive to adulthood, but have very similar elevations of the same blood metabolites seen in propionic acidemia patients. These include elevations in propionylcarnitine and methylcitrate as well as increases in glycine, alanine, lysine, and ammonia. We have also observed evidence of cardiac dysfunction and possible heart failure in the mice suggesting that they also share this symptom.

Our findings highlight the diverse nature of PA presentation. Elevations in circulating propionylcarnitine and methylcitrate are nearly universal in affected individuals, but other aspects of the disease are observed less frequently. Different organ systems are implicated in different people, for instance neurological symptoms are common and manifest as seizures, developmental delay, lethargy, and hypotonia. In the heart it is common to see arrhythmias and cardiomyopathy even in young PA patients. Many of these symptoms are worsened by noncompliance with protein restricted diet regimens or stress to the body caused by infection.

Although dietary treatment has greatly improved the prognosis for PA patients, few other treatment options have been developed. Liver transplantation has emerged as a viable therapy option for PA, but transplant operations carry a certain degree of risk themselves. Anesthesia to begin the operation may by itself make this approach unsafe for certain PA patients. After liver transplantation, life-long immunosuppressant drugs will be needed to prevent rejection of the donor liver. Immunosuppression may also increase the risk of infections that may also drive metabolic crises.

Given these issues, we have worked to develop safer and less invasive treatment options based on gene therapy with viral vectors. To date we have treated adult mice with adenoviral and adeno-associated virus (AAV) vectors expressing the gene for human PCCA. We demonstrated in an article titled "Generation of a Hypomorphic Model of Propionic Acidemia Amenable to Gene Therapy Testing" published in the journal *Molecular Therapy* (2013) that both of these gene therapy vectors significantly reduced propionylcarnitine and methylcitrate levels in the blood of the mice within one week of treatment. We are pleased to note that propionylcarnitine and methylcitrate levels have remained low for over a year-and-a-half after treatment with a single dose of AAV in male mice suggesting that the therapy can last for long periods.

One practical note that may interest parents of children with PA is the fact that gene therapy in the mice appeared to rapidly improve the ability of the animals to consume normal protein-containing food. Indeed, within one week

(continued on page 4)

BARRY LAB UPDATE (CONTINUED FROM PAGE 3)

of therapy, the body weights of the animals increased drastically. This bodes potentially well for this approach having positive day-to-day impact should we be able to translate this towards treating PA patients.

New Studies

The varied presentation of PA across several organ systems has caused some investigators to examine where the cause of these symptoms lie. Previous studies have shown that certain protein complexes in the mitochondria of heart tissue are lower than in individuals without PA. Since the mitochondria are responsible for providing most of the energy used by cells in the human body it is thought that this could lead to a lack of energy available to the heart and result in cardiomyopathy. It is also unclear exactly what effect circulating levels of propionylcarnitine and methylcitrate have on the body and we are not sure to what degree different tissue types contribute to the circulating levels of these compounds.

Our most recent study using our A138T PA mouse model was designed to help clarify some of these questions. In September of this year (2014) we published a new research article in the journal *Human Gene Therapy* titled "Effects of Adeno-Associated Virus Serotype and Tissue-Specific expression on Circulating Biomarkers of Propionic Acidemia." Our group and others have observed that different serotypes of AAV are more apt to deliver genes into the liver, heart, or cardiac and skeletal muscles in mice.

For example, AAV1 is better at delivering genes into muscles and AAV8 is better at delivering genes into the liver. We made these vectors totally specific to the muscle and liver and then compared how well they could treat the PA mice. Under these conditions, both vectors improved metabolic levels, but the liver-specific gene therapy reduced systemic metabolites better (**Figure 1**). In many ways, the AAV8 liver-specific gene therapy is analogous to transplanting the liver, except we perform a simple injection rather than invasive surgery and do not have to apply immune suppression. Conversely, gene therapy is more experimental than transplantation, so safety still needs to be evaluated.

Reduction in the methylcitrate levels shown here is encouraging because it is hypothesized that high levels of methylcitrate in tissue could be a possible cause for the energy deficiency mentioned in the heart and has been correlated with high ammonia levels in the brain as well.

While liver-targeted gene therapy reduced metabolites in the blood better, in more recent work, we have found that the muscle-targeted vector was markedly better at repairing the heart. For example, AAV1-PCCA corrected signs of cardiac dysfunction, but AAV8-PCCA did not.

These data suggest that gene therapy that repairs PCC in as many tissues as possible is better than therapies that only repair it in one site. This is consistent with observations that liver transplantation can blunt certain symptoms, but may not always improve others like cardiac effects in PA patients.

Our Future Plans

Since the liver is the main metabolic organ in the body, it will need to be treated by gene therapy or by transplantation. These studies also demonstrate that there are potentially harmful compounds being produced by the muscles and that gene therapy in the muscle reduces systemic metabolite levels, but also reduces cardiac symptoms. These data suggest that tissue targeted gene therapy or transplantation are not the best approach to address the spectrum of PA disease effects in different tissues. Therefore, we are moving forward to improve AAV vectors that deliver genes to many tissues after intravenous injection.

In addition, we are working to use the mice to better understand the neurologic consequences of PA and to determine if direct neurologic gene therapy will be needed. Our PA mice have a number of symptoms that indicate that the disease is impacting their brains. Since we can't speak to the mice, these symptoms are unfortunately difficult to assess. We are therefore embarking on a number of studies to explore if the A138T mice are a good model of the neurologic aspects of PA. The mice have high levels of ammonia in their bloodstream and we are working to determine how the circulating ammonia or methylcitrate produced locally in the brain may affect the disease. There are similar questions to those we have addressed in the heart that must be addressed in the brain as well. Do we need to treat the brain specifically or will systemic treatment of the liver and muscles alleviate brain symptoms? What is the most effective way to treat the brain with gene therapy? Fortunately the AAV vector system will allow us to explore different options, and we have excellent collaborators that are helping us address these issues.

NICHOLAS' STORY

My son Nicholas was born at 31 weeks gestational due to IUGR. He spent 85 long days in the NICU over at Strong Memorial Hospital in Rochester, NY.

When Nicholas was born luckily he did not require any oxygen or serious medical attention, it was a few weeks later in the NICU when the newborn scan had come back with some "odd results." With a second repeat to the newborn scan it was diagnosed my son had Propionic Acidemia. Although nothing else indicated that he had PA the Genetics doctor insisted we treat him accordingly to the results.

As he was maturing in the NICU he had to go under surgery because he developed Necrotizing enterocolitis (NEC) the surgery and the PA worked against each other and caused my son to be in critical condition for 3 weeks post surgery. Once he finally healed up things began to look a lot better, he had such an appetite for his bottle, and "shocked" the genetics team with how much he wanted to eat. Post NICU we had our son home and things felt normal. Nicholas got his colostomy bag off and that bettered his ammonia levels, which resulted in him no longer having to take Carbaglu (ammonia decreasing medicine.)

At the 9 month check up, the Genetics team thought he was doing great with eating all his fruits and vegetables and decided to add on "pastas and grains." Nicholas was given a goal of eating up to 6-7grams of protein a day.

He is now almost 11 months old and loves food! He has quite the appetite and will eat anything he may come across, which we keep a careful eye on. Developmentally doctors have no concerns as of now and is doing well. As his one year birthday approaches we have talked with his genetics dietician and will continue to increase his protein intake as his body allows. It's been a roller coaster this first year but we are happy to be in a "safe" place now with Nicholas and his happy/silly personality!

BIOMARKER RESEARCH OPPORTUNITY (NO TRAVEL REQUIRED)

Individuals of any age with propionic acidemia who have not had a liver transplant may be eligible to take part in a research study on biomarkers being done by Dr. Loren Pena at Duke University Medical Center.

All information and samples (blood and urine) for the research study will be taken during regular visits to a geneticist/ metabolic physician and during times of hospital admission. No extra visits to a doctor are needed.
Information and samples will be sent from the geneticist/metabolic physician to the research staff at Duke.
The cost of sending samples to Duke will be covered by the study. You will not be paid for taking part in the study.

Study goals
Biomarkers are compounds that can be measured by laboratory tests in body fluids such as blood and urine and are helpful in predicting disease states. For example, cholesterol level is a biomarker for heart disease. For patients with some metabolic disorders, biomarkers can be helpful in guiding treatments (such as the amount of protein a person can eat) and can predict whether a person is at risk to develop a health problem associated with that metabolic disorder. Currently, there is no standard set of laboratory tests recommended to help guide treatment for people with propionic acidemia. This is because little is understood about which biomarkers are most helpful. The goals of this study are:

To better understand how different biomarkers can be used to guide treatment in people with propionic acidemia
To investigate whether a specific disease process called oxidative stress is involved in propionic acidemia
To look at specific risk factors for pancreatitis in people with propionic acidemia.

For more information, please contact:
Jennifer Goldstein, PhD, CGC
Study Coordinator
Phone (919) 684-0626
jennifer.goldstein@duke.edu

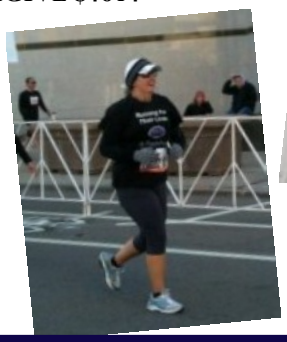
PAF EVENT & FUNDRAISING SPOTLIGHT

UPCOMING EVENTS AND CAMPAIGNS

- Ongoing- **Annual Appeal**– Goal $15,000!

PAST EVENTS AND CAMPAIGNS

- 5/2014- **Luftman, Heck & Associates**, **B-F.R.E.E. 2014 Winter Fitness 1st Place**, Columbus, OH, $1500
- 5/2014- **Wingfest**, Milwaukee, WI, $424
- 5/4/14- **Bretty's Bunch Broad Street Run**, Philadelphia, PA - $1977
- 8/23/2014- **Ann and Hope Deddens fundraiser for PA Foundation,** They had food, lots of activities for kids, and, after dark, a movie under the stars, St. Louis, MI, $1150
- 9/20/14- **9th Annual Tailgate Party & Corn Hole Tournament for PAF,** Gahanna, OH**,** $8967+ GwenForACure.com (Allison & Gwen, right)
- 10/19/14- **Tara Gerlach, Pounding the Pavement for PA, Columbus Half Marathon**, $560+ (middle, right)



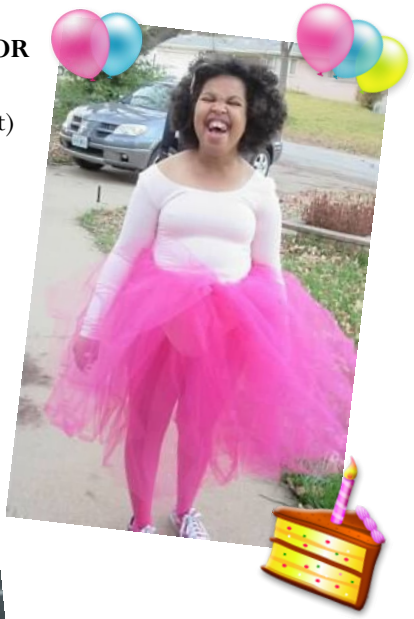
DONATIONS IN MEMORY

- **Nicholas Phillips**
- **Patricia Scott, Kate's grandmother**
- **Sally Workman, Chase's grandmother**

DONATIONS IN HONOR

- **Varun Gattupalli**
- **Nalani Johnson** (right)
- **Kate Lowry**
- **Gwen Mouat**
- **Allison Ellis**

GOODSEARCH $1407
IGIVE $4014



CARBAGLU STUDY IS EXPANDING

Our trial of Carbaglu during acute hyperammonemic crises in patients with PA and MMA as well as certain urea cycle disorders is now open at 7 US sites: Boston Children's, Rainbow Babies and Children's Hospital of Cleveland, The Children's Hospital of Colorado, Children's Hospital UCLA, Children's Hospital of Philadelphia, Children's Hospital Stanford, and Children's National Health Center.

We anticipate opening soon at two additional sites: Mount Sinai Hospital and Children's Hospital Pittsburgh. To date, we have enrolled 8 subjects, and have accumulated data from a total of 29 hyperammonemia episodes. However, we are still far from our goal of a total of at least 150 hyperammonemia episodes, and hope to continue enrolling eligible patients to our study. Patients with propionic acidemia are eligible for the study if they are primarily treated at one of the above sites, and have had an ammonia level at any time greater than or equal to 100 micromoles per liter.

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.*

PAF ANNUAL REPORT

FINANCIAL REPORT

Revenue:
Contributions: $62,042
Interest Income: $124
In Kind Donations: $724

Total Revenue: $62,890

Expenses:
Research Grants/Registry: $31,398
Programs & Outreach: $862
Printing (in-kind): $724
Fundraising: $621
Management & General Expenses: $1,241

Total Expenses: $34,846

Cash Assets 8/1/2013: $117,370
Cash Assets 7/31/2014: $145,413
Note: Off $1 due to rounding

PROGRAM ACCOMPLISHMENTS

Research: Grant Disbursement:
$28,697 Loren Pena, M.D., PhD., Duke University, Durham, NC, "A prospective study of biochemical parameters reflective of metabolic control in propionic acidemia"

Outreach:
Distributed fall and spring newsletters to affected families, clinicians, and donors

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Board disclosure:
Donations made by board members totaled $704

We want to hear from you! Have a PA story to tell, event to promote or news? Fall newsletter submissions due by February 1!

Help Us Find the Cure!

*Name*_____

*Address*_____

City, State, Zip _____

*Phone*_____

*E-mail*_____

Please send an acknowledgement to:

*Name*_____

*Address*_____

*City, State, Zip*_____

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

If you work for a company that has a matching program, please include the matching form.

Please mail your check made payable to: Propionic Acidemia Foundation 1963 McCraren, Highland Park, IL 60035

Thank you for making a difference.

SEARCHING FOR A CURE
HOPE FOR OUR CHILDREN

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PROPIONIC ACIDEMIA FOUNDATION

Propionic Acidemia Foundation is run 100% by volunteers and we couldn't do it without you

Please email paf@pafoundation.com to join a committee.

PAF VOLUNTEERS AND BOARD MEMBERS ARE NEEDED!

PAF@PAFOUNDATION.COM

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