

# Propionic Acidemia Foundation

VOLUME 1, ISSUE 2

APRIL 2007

## FOUNDATION NEWS

Welcome to the second edition of the PAF newsletter. In October, 2006, PAF received 3 applications for research grants. Our Medical Advisory Board recommended that we fund all 3 requests and we are thrilled to announce that we have offered \$85,000 in research grants. You can read more about the promising research PAF is funding on Pages 2 and 6. All of this could not have been achieved without your help. Thank you. This is just the beginning. We are hopeful that PAF will be able to continue to fund researchers devoted to finding better treatments and a cure for PA and know that our dream will become reality with your help.



PA  
Family  
Day  
2006

## PA FAMILY DAY AUGUST 11TH 2007

On August 11th, we will have our second PA Family Day in Highland Park, IL (just outside of Chicago). There will be lots of fun things for the kids to do and plenty of low protein

foods. What a great opportunity to be around a community of people who experience the daily life of PA. All PA families and friends are welcome.

For more details and to RSVP contact Jill at:  
1-877-720-2192 toll free  
[paf@pafoundation.com](mailto:paf@pafoundation.com)

### Volunteers Needed

PAF is looking for volunteers. There are several projects that PAF is working on that could use your help including fundraisers and donations. (see page 3) If you are interested in volunteering some time to the PAF please contact us through email or our toll free line.

We look forward to hearing from you!

[paf@pafoundation.com](mailto:paf@pafoundation.com)  
1-877-720-2192 toll free

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## MUSCLE-BASED APPROACH FOR GENE THERAPY

PAF just awarded Dr. Wolff a \$30,000 grant for this promising approach to gene therapy.

Gene therapy promises to be a treatment for people with propionic acidemia by correcting the disorder at its most basic level. It involves transferring the normal gene into the cells of the patient so that they could metabolize propionic acid. It is anticipated that patients treated by gene therapy would be able to tolerate more protein intake or depending on how successful, even liberalize their protein intake substantially.

So that is the promise, but what is holding back this promise. It is the ability to safely deliver the propionic acidemia-related genes into the appropriate target cells. Gene therapy (at this time) can really only target certain cells in the body. Given the central role of the liver in propionic acidemia, this has been a prime target tissue for gene therapy. However, gene transfer into the liver has been challenging. For example, an adenoviral vector was used to deliver a gene into the liver to treat another metabolic disease (OTC deficiency) and this led to the patient's death. More recently, another type of viral vector, an AAV vector, was used to deliver a gene to the liver to treat another genetic disease, hemophilia, but this caused some liver toxicity and the trial was stopped. While liver-based gene therapy approaches for propionic acidemia are definitely a promising avenue for further work, gene delivery techniques for the liver have to be further perfected.

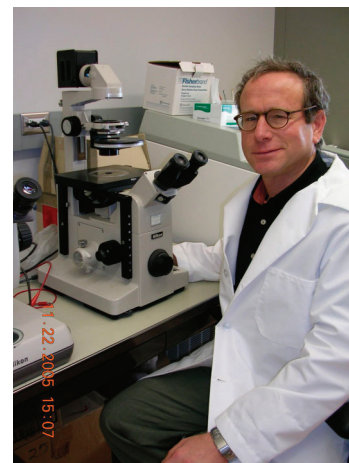
Muscle is another tissue that could be a suitable target for treating propionic acidemia. In addition, it appears that gene delivery techniques into the muscle may be safer. Jon Wolff and his

colleagues have developed a technique by which many muscles throughout the limb can be targeted by delivering a gene via the blood vessels. Using this regional intravascular

approach, the gene can be carried into the muscle cells either by the use of AAV vectors or by the use of naked plasmid DNA. Each of these two approaches have their advantages and disadvantages. Using a genetic mouse model for propionic acidemia, Jon Wolff and his colleagues will be exploring how effective a muscle-based approach for gene therapy could be.

Human clinical trials involving the intravascular delivery of AAV vectors and naked plasmid DNA are being planned for Duchenne muscular dystrophy. These studies will provide important data about the safety of this approach. If a muscle-based approach for propionic acidemia is effective in the mouse model and the intravascular muscle techniques are safe, then a human clinical trial for patients with propionic acidemia will be done.

By Jon Wolff, UW Madison



Thank you to our Corporate Sponsors:

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## EASY IDEAS FOR FUNDRAISING

MissionFish is a non-profit organization working with ebay to help other non-profit organizations, like the Propionic Acidemia Foundation, raise needed funds. Here is how it works:

Any ebay user lists an item they have on ebay

They register their ebay account ID with MissionFish ([www.missionfish.com](http://www.missionfish.com))

They list their item on ebay, selecting the Propionic Acidemia Foundation (PAF) as the organization to benefit from the auction, including the amount as a percentage or dollar amount of the selling price

Once the item is sold and the seller receives payment, the seller sends the money to the PAF

Then ebay refunds part of the fees that the seller paid to list the item

MissionFish will then send the seller a letter thanking them for the donation.

Over \$33 million has already been raised through MissionFish.

Clean out your closets today and help find better treatments and a cure for tomorrow!

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It is because of our generous donors, both individuals and organizations, that we are able to provide support to those affected by Propionic Acidemia (PA) and research grants to those looking to improve the lives of those with PA. In order for more of our budget to go to programs the Propionic Acidemia Foundation could use the following items:

Stamps

Empty inkjet cartridges

HP 56 ink cartridges

HP 94 ink cartridges

Thank You cards

Avery Inkjet Postcards, #8387

Samsung ML-2510 Toner

Gift cards to Staples, Office Depot, or Office Max

Underwriter for small printings of brochures, etc.

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Thank you for using iGive.com and raising over \$800.00. Please tell everyone you know that likes to shop on-line about this easy way to fundraise.

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In the past year, PA Families and Friends have used [www.goodsearch.com](http://www.goodsearch.com) over 14,000 times to raise over \$140.00 for our cause. Keep searching and telling everyone you know about Goodsearch and Propionic Acidemia Foundation.

For more information, email PAF at [paf@pafoundation.com](mailto:paf@pafoundation.com).



LOOKING FOR  
OTHER  
FUNDRAISING IDEAS?  
CONTACT PAF  
FOR OUR NEW  
FUNDRAISING  
PACKET.  
EVERYTHING YOU  
NEED TO SUCCEED!



## PA FAMILY SPOTLIGHT— GWENDOLYN GRACE MOUAT

My daughter, Gwen (Gwendolyn Grace Mouat), was born Feb 3, 2006 & we have just celebrated her first birthday! Much to my surprise, it was a bittersweet day for me. I found myself reflecting upon her traumatic first days of life, her close calls with final mortality, the 15 hospitalizations, the effects of stress on our family, & the age lines that have appeared on my face. But as I said, it was a bittersweet day & the sweet thoughts were both very real & almost unexplainable. Gwen's ammonia peaked at 1,500 when she was 3 days old & she's been very sick many times since then; but she's not only pulled through the first year of the storm, she's become a very happy & beautiful little girl. She says "MaMa" & "DaDa", started crawling on Christmas Day, pulled-up onto her feet on her 1st birthday, & giggles hysterically when playing with her 3 year-old brother Robbie. This has only been one portion of the miracles we've experienced this past year, as I will try to explain further.

When Gwen survived her initial crisis, I knew God had spared her life for a reason. That reason became apparent to me around the time I had lunch with Michelle Ellis (local PA mom of 14 month-old Allison.) We talked about the stress in our lives & the uncertainty of it all for most of the hour, but toward the end, our topic switched to treatments for PA (or lack thereof.) Michelle mentioned her friend Meredith had asked people to donate money to the PA Foundation in lieu of birthday gifts. She raised about \$275. We decided to meet again to talk about more fundraising ideas. I asked a few neighbors, some good friends, & some family members to join our committee, & we scheduled our first meeting at my house. We created fliers to hand out to the 600 houses in our neighborhood, advertising 2 upcoming events. We emailed an anchor at a local news station to cover our events & she called us back! Finally, we sent an email with event fliers attached, to everyone we knew, asking them to attend our fun events.

Before I go on, I must add that not everyone we contacted was excited to help. I was surprised at how few responses were returned from our fliers & emails. Admittedly, this took away some of my motivation, but the first event was already in the works, many people were signing up to help, & the only way to go was forward. The lesson I learned is if you tell 100 people, you will find 10 who want to help & if you tell a million people, you will find a few

thousand who want to help.

Michelle hosted our first event, a scrapbook day at Archiver's, & raised \$1000. Our second event, a CornToss Tournament with raffles & a silent auction, raised \$7000. We were elated beyond words, but more importantly, we learned about the incredible caring people in our lives & the people in our community who wanted to help us on our mission. By the time our third event took place, we had more people asking to volunteer & three fundraisers that occurred without our assistance. Since our first official event in August of 2006, we've collected over \$30,000 for the Propionic Acidemia Foundation and had at least 15 other events including several from Dublin Jerome High School and Dublin Scioto High School. They have ranged from simple events like making a donation in lieu of gifts for birthdays to our "Lights of Love" campaign which raised almost \$6,000. (see photos on the right)

With my husband & I both working full-time, having no immediate family in town, & two small kids, our "free time" is very limited. As you can imagine, we've struggled as a family with the amount of time I have dedicated to the fundraisers. Many people say to me "You're a Super Mom", but I am nothing of the sort. All I am, is a mom who desperately loves her little girl & who wants to make a difference in her life & the lives of countless others. I find hope in my heart, knowing that I am raising awareness of this disease & so many like it. I find joy in my life from spending time planning these events with my very closest friends. If the day comes that Gwen should pass before me, I'll have peace in my soul, knowing that she has peace & I helped fulfill God's wishes with one of her many purposes in life; by doing what I could to help further research and bring years to the lives of other children.

Please visit our website [www.GwenForACure.com](http://www.GwenForACure.com) for more photos & information about our events. Do not hesitate to contact me with any questions or suggestions.

Most Sincerely,

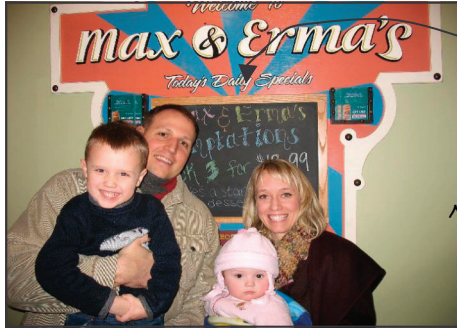
Jennifer Mouat,

Mom to Gwen (PA, age 1)

[Jen@GwenForACure.com](mailto:Jen@GwenForACure.com)

614-775-0687

# GWENDOLYN GRACE MOUAT



Jen, Tom,  
Robbie & Gwen  
celebrate  
PA

The FUN in  
fundraising! Friends,  
smiles & good times!

moms Brittany,  
Michelle and Jen



(Our faces are  
frozen

From 710 to 5,721  
Lights of Love!

Men's winner of the 5K  
(Happy squirrels!)



Perfect



(We're going for "Griswold" next year!!)

Cornhole co-champs  
(they had so much fun  
they gave the \$ back)  
we love you guys!



YAY! We finished.

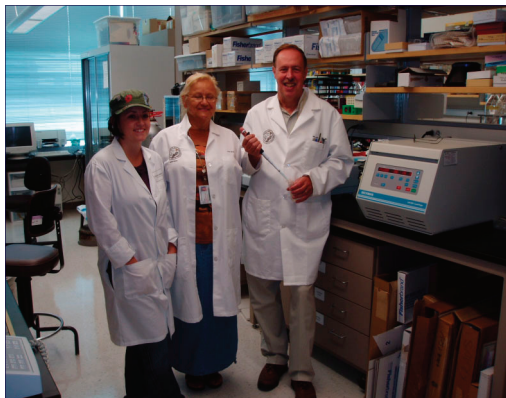


PA families unite!  
Jill, Mouats,  
Ellises with twins,  
Allison & Austin



PA dad, Tom, kicks off the CH  
Tournament with an inspiring speech!

## CHAPERONE STUDIES IN PROPIONIC ACIDEMIA



Propionic acidemia (PA) is a devastating disease with one third of affected infants dying in early infancy. PA is caused by a deficiency of an enzyme called propionyl CoA carboxylase or PCC for short. The deficiency, in turn, is caused by changes (mutations) in one of two genes that determine how this complicated enzyme is made. If each parent has one mutation in the same gene then there is a 1 in 4 chance that the child will inherit both of the mutations and be affected with the disease. We are currently the only laboratory in the world that systematically studies the biochemistry

and molecular genetics of this disorder. In other words, we determine which patients are affected with the disease and what mutations do they carry. We are also trying to show how the mutant enzyme subunits can be properly folded before PCC is assembled. To be biologically functional, PCC, which is composed of six alpha and six beta subunits, must assemble and fold correctly inside the cell. Some mutations are known to affect the ability of the subunits to fold, and when this happens little or no functional PCC is made. We are screening a large number of chemicals called chaperones to see which ones prevent the mutant enzymes from not folding properly and becoming inactive. We have so far found that some of the chaperones allow some of the mutant enzymes to become fully active but we have a long way to go. There are over 100 mutations to go through and there are many chaperones to test. We have done this by using a bacterial expression system in which mutant PCCs are able to interact with the chaperones. Later on, we will have to test if the chaperones work in patient cells obtained from their skin. Our hope is to be able to develop a treatment using this approach that will clinically benefit a number of PA patients in the future.

**By Jan P. Kraus Ph.D. Professor, Department of Pediatrics UCDHSC at Fitzsimons**

## GENE THERAPY FOR PROPIONYL COA CARBOXYLASE -UPDATE

The Barry Laboratory at the Mayo Clinic is working on a project to test if gene therapy can be used to treat propionic acidemia (PA). To test this, PA mice from Dr. Miyazaki are being used as subjects for delivery of the PCCA gene to their livers. One of the PA mouse models has both copies of the PCCA gene knocked out. These mice are born normally, but do not survive past 36 hours due to total absence of functional enzyme. The Barry laboratory has very recently shown that at least some of these mice can be rescued from death and their lifespan extended by delivering gene therapy within hours after birth. This data is very preliminary, but holds promise for a genetic intervention to suppress the metabolic disruptions due to the disease. Work is underway to validate these findings and determine the duration of genetic correction and how this affects global metabolism and function in the mice.

**By Michael Barry, Ph.D, Mayo Clinic**

## THE SWEETMAN FAMILY

Our son, Ben, was diagnosed with PA at 17 months after going into a metabolic crisis. He was a full term baby with no signs of any illness until then, so his diagnosis was a surprise. At that point he wasn't walking on his own yet, which was really the only physical sign of his disorder. We started PT and OT right after he was diagnosed and between the therapy and his change in diet, he was walking by 19 months and has flourished ever since. He is now four years old. We have continued PT and OT twice a month each. His therapists think his physical capabilities are close to what is appropriate for his age, but he still does have some weaknesses from the low muscle tone. Ben's cognitive development has been right on track as well as his speech. He does have a restricted diet of 17 grams of protein a day. He also drinks about 21 oz. of Propimex-2 and Prophree a day. He has been able to eat most normal foods up until recently. We feel like his limited diet leaves him hungry sometimes, so we have started to introduce some low protein foods, and so far he has liked them.

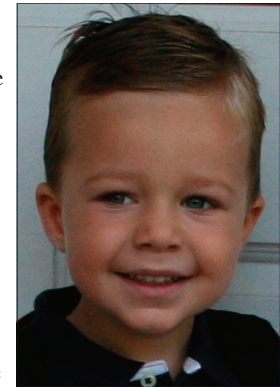
Ben goes to preschool two days a week and loves it. He brings his own snack and is learning that his tummy needs special things that are low in protein. We are really proud of him for learning that he is different and think it is important



that he continues to take ownership of this disorder. He is also involved in other activities such as gymnastics, swim lessons, ski lessons, and

is going to start ice skating next month. We have tried to get him involved in anything that will help him get stronger.

Exposure to germs and illness is a worry for us, but we just try to be really diligent about handwashing. Over the years, Ben has been in the hospital four different times needing IV fluids due to illness. His last hospitalization was 14 months ago. We feel so fortunate that Ben is doing so well and thank God each and every day.



Ben Sweetman (PA)

Our family was blessed with the birth of a healthy baby girl, Maggie, last May. We decided that a 1 in 4 chance of having another child with PA was just too risky for us, so we opted to do In-vitro Fertilization with Pre-genetic Implantation. We flew to Chicago to work with Dr. Ilan Tur-Kaspa at the Reproductive Genetics Institute. This process entailed fertilizing each egg and growing it to a certain number of cells. At that point, a cell can be safely removed and analyzed to see if the embryo has PA, is a carrier, or is totally unaffected. We ended up with three unaffected embryos, a few embryos that stopped growing on their own and seven that were affected with PA. We chose to donate those seven to genetic research specific to PA. We implanted one of the unaffected embryos, which was Maggie, and chose to freeze the other two. We will try to implant them as well. There is a 50% chance an embryo can survive the thawing process and then about a 30% chance that a woman will become pregnant. So, with those percentages, it is evident the process does not come with a guarantee, but we did have a wonderful experience resulting in our miracle baby.

SEARCHING FOR A CURE  
HOPE FOR OUR CHILDREN

Propionic Acidemia Foundation  
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We would like to thank our Medical Advisory board for all of their support, input, advice, and knowledge. We could not do it without you.

We would like to acknowledge and thank each of you personally for making a difference for families affected by Propionic Acidemia.

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