

HELP US FIND THE CURE!

The **Propionic Acidemia Research Network (PARnet)** endorses donating to the **Propionic Acidemia Foundation (PAF)**, a 501(c) 3 non-profit organization that funds academic and clinical research to find better treatments and ultimately a cure for PA. Donations are distributed to PAF Medical Advisory Board approved research projects.

All US contributions are tax-deductible.

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■ other currency

I work for a matching gift company and have enclosed the necessary form for matching.

I would like more information or to help. Please contact me.

Checks can be made out to **Propionic Acidemia Foundation** and mailed to:

In the United States:

PARnet-USA
PAF Research Fund
10305 Hansa Cove
Austin, TX 78739

In Europe:

PARnet-UK
PAF Research Fund
30 Morningside Avenue
Aberdeen AB10 7LX UK

For research information and current PA projects:

Visit **Propionic Acidemia Research Network** at
www.paresearch.org
and

Propionic Acidemia Foundation at www.pafoundation.com

Thank you for taking time to read about our cause
All donations count in finding a cure!

CURRENT PA RESEARCH

The Use of Chaperones to Enhance PCC Assembly and Expression and PCC Purification

**Dr. Jan P. Kraus, Ph.D. Dept. of Pediatrics,
University of Colorado School of Medicine,
UCDHSC, Aurora, CO**

Efforts are underway in the Kraus lab to understand how the enzyme PCC is assembled *in vivo* and to find options for correcting PA mutations that are defective in PCC assembly. Dr. Kraus is also purifying PCC that may be used to treat PA in the future.

Liver-targeting Adenoviral Vectors for PCCA delivery

**Dr. Michael A. Barry, PhD., Mayo Clinic,
Rochester, MN**

Dr. Barry's lab is currently constructing and testing biotinylated adenoviral vectors for liver-specific targeting of PCCA for PA gene therapy.

Correction of Novel Splicing Mutations in PCCA and PCCB

Dr. Magdalene Ugarte Ph.D., Dpto. Biología Molecular, Universidad Autónoma de Madrid, Madrid, Spain

The Ugarte lab has a long history of PA mutation identification and DNA analysis. Patients with splicing mutations in PCCA or PCCB have the potential of being treated if drugs can be developed to correct certain cellular splicing defects.



**PROPIONIC
ACIDEMIA
RESEARCH
NETWORK**

*Uniting Academics and Medicine
To find a Cure*



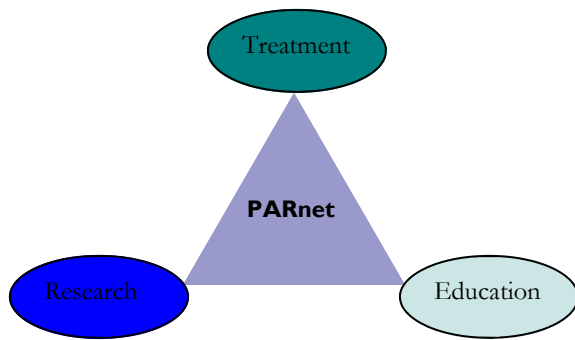
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Propionic Acidemia Research Network (PARnet)

Mission

The mission of **Propionic Acidemia Research Network, (PARnet)**, is to identify key medical and research issues relating to propionic acidemia (PA); facilitate communication about these issues among physicians, educators and the research community; and provide financial resources that result in creation and availability of new treatments and eventually a cure for PA.

Importance of Success

Propionic acidemia affects patients and families in devastating ways - physically, financially and emotionally. The cost of caring for a PA child increases each year. Medical systems will continue to be taxed and families will be heavily burdened until we have a cure for this disorder.

PA is a multi-faceted disease caused by over 100 known genetic mutations which has made genotype/phenotype correlations very challenging. We believe, however, if just a few of the many brilliant minds from the academic research and medical communities focus on this challenge, a real cure for this disease can be found.

PARnet is seeking motivated researchers, laboratories and physicians who will work with us to conquer this deadly and often debilitating metabolic disorder.

What is PA?

Propionic Acidemia is an autosomal recessive genetic disorder of amino acid metabolism. In the U.S. it is estimated that PA strikes once in every 50,000 births and is the most common of the organic acidemias. PA is caused by a deficiency in the enzyme propionyl-CoA carboxylase (PCC). **Mutations in either of the genes PCCA or PCCB can result in a child developing PA.** When someone with PA consumes a high protein diet, their enzyme deficiency causes every cell in their body to produce propionic acid, methyl citrate and other toxins which attack vital organs such as the brain, liver and heart. Today, PCC can not be supplied to PA patients the way insulin is supplied to someone with diabetes, causing metabolic regulation to be tricky and difficult to manage.

Daily Management of a PA Child

Imagine trying to manage a child with diabetes without the help of insulin! All foods with sugar would be monitored to avoid illness. Management of a PA child is similar, but instead of sugar, caregivers monitor all protein consumed. A delicate balance is required for growth, since consuming too much protein can lead to ketoacidosis and metabolic decompensation. To complicate matters, most PA children also refuse oral intake and must be tube fed a protein-restricted formula that provides the exact amount of protein, calories and water they need.

Each day PA patients perform a continual balancing act of protein metabolism without the correct amount of PCC available in their bodies. 24/7 management of a PA child is therefore quite stressful for caregivers, since any episode of metabolic illness can result in permanent neurological damage.

Current Medical Treatment for PA

Diet control may sound simple, but is in fact very complicated and is an inadequate way to treat PA. Each person produces a unique amount of PCC and requires a different amount of protein - making it impossible to construct a common or consistent PA diet to prevent toxins from forming. Supplemental L-carnitine is administered to combat secondary carnitine deficiency, and biotin, the vitamin co-factor for PCC is also frequently prescribed to enhance enzyme activity.

The avenues for propionic acidemia research are varied and are waiting for more researchers to discover!

Research Focus

- **A GLOBAL PA PATIENT REGISTRY** is needed so all metabolic geneticists and researchers can easily access genotype/phenotype data
- **ESTABLISHMENT OF CONDITIONS FOR SUCCESSFUL STEM CELL TRANSPLANTATION** and confirmation of long-term production of PCC in the liver
- **CONSTRUCTION OF VIRAL VECTORS THAT DELIVER PCCA OR PCCB DIRECTLY TO THE LIVER** while avoiding other tissues
- **CHAPERONE PROTEINS** aiding in the assembly of PCC may be a key to correct some PA mutations
- **ANALYSIS OF SPLICING MUTATIONS** in PCCA and PCCB that produce some low level wild-type mRNA may provide clues to treat these mutations
- **LIFE-THREATENING CARDIOMYOPATHY** demands answers to its cause(s) and options for prevention
- **NEW GRADUATE STUDENTS, MEDICAL STUDENTS AND POST-DOCS** need to look at these issues and consider pursuing projects that will generate a gene therapy for PA

Coriell Institute for Medical Research

PARnet, in conjunction with the Propionic Acidemia Foundation endorses the establishment of a PA DNA and Cell Repository at Coriell Institute for Medical Research.

The Human Genetic Cell Repository (HGCR), established in 1972 by the National Institutes of Health (NIH), collects, stores and distributes cells and DNA to researchers worldwide. Currently, the HGCR is collecting blood and skin samples from PA patients and their families to create confidential PA cell lines. For more information go to www.paresearch.org, and to www.pafoundation.com.



You can help further PA research by donating a genetic sample that will be available to any researcher interested in studying PA