

The National PKU Alliance is pleased to announce its 2013 Research Awards! These awards are made possible by our member organizations who raise funds each year on the local level for research. Thank you for helping make these awards possible as we work towards improving treatment options for PKU and accelerating the timeline for a cure.

Research Grants



Dr. Shawn Christ, Associate Professor of Psychological Sciences and Associate Director of the Brain Imaging Center at the University of Missouri, will examine the effects of PKU on gray matter structures in the brain. Previous research on PKU and neuroanatomy has focused

almost exclusively on the white matter connections of the brain. In comparison, little is known about the potential impact of PKU and increased phenylalanine levels on gray matter structures of the brain. Whereas white matter is implicated primarily in the transfer of information, gray matter regions are where the processing of the information occurs. Dr. Christ will apply recent advances in neuroimaging to analyze and compare high-resolution MRI images from a sample of individuals with PKU and a comparison group of individuals without PKU. The pilot data/results generated will be used to secure additional funding for a larger, more comprehensive study of PKU and the brain. Hopefully this line of research can be expanded to study how the impact of PKU on the brain is moderated by treatment factors (e.g., dietary phe restriction, LNAA therapy, administration of sapropterin) and how this relationship may further differ at different times in development (e.g., early childhood, adolescence, adulthood).

Dr. Donna Santillan's lab at the University of Iowa Hospitals and Clinics has been developing an artificial organ system by encapsulating HepG2 cells to treat PKU. The goal of the treatment strategy is to reduce the burden of the diet and blood Phe monitoring for



people with PKU. Additionally, as a research group in Obstetrics, the lab is particularly interested in using this system to treat maternal PKU since the encapsulated cells have been shown to last for up to a year, and could thus be used in pregnancy in PKU women to prevent maternal PKU Syndrome. In the initial studies of this treatment for PKU, as well as for preventing maternal PKU, Dr. Santillan will measure how much the Phe is reduced in the mouse model of PKU, how long the artificial liver reduces Phe, and whether subsequent re-administrations of the therapy are as successful as the initial treatment.

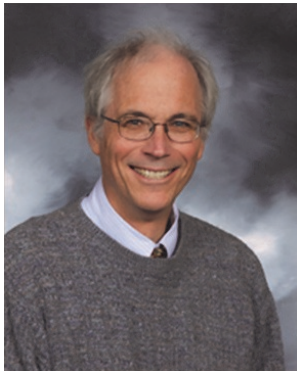


Dr. Ione von Herbing, Associate Professor, Department of Biological Sciences, University of North Texas, Denton, TX & **Katherine Deming**, MS, Ph.D. Candidate and Project Leader will continue their innovative study entitled, "Genetically Engineered Probiotics for the Treatment of PKU." The goals of the research are: 1) to a use

a genetically engineered probiotic bacteria, *L. reuteri* to catabolize phe *in vitro* and, 2) use the created probiotic in the PAHenu2 mouse model to determine the efficacy of this new probiotic *in vivo*. By reducing the amount of phe that can enter the blood stream from the food, the toxic build up of phe in the blood will be prevented. The resulting outcome of this study will hopefully be to allow animals, and subsequently PKU patients to eat a "normal" diet by allowing the altered probiotic bacteria to compensate for their lack of functional PAH.



Research Grants Cont.



Dr. K. Michael Gibson's research will continue to focus on an approach to PKU therapy that examines the ability of non-physiological amino acids (NPAAs) to lower brain phe levels and thereby restore brain amino acid equilibrium. The NPAAs inhibit the shuttle systems that move large

neutral amino acids (including phenylalanine) from the blood into the brain. The main component of this shuttle system is the type 1 LNAA transporter (or LAT-1). When blood phe levels are elevated, phe is preferentially transported into the brain to the detriment of other LNAAs because it oversaturates the LAT-1. This may result in serious chemical imbalances in brain, because some LNAAs are the precursors of key neurotransmitters and cofactors, including dopamine (DA), serotonin (5-hydroxytryptamine (5-HT)) and Sadenosylmethionine (SAME). DA and 5-HT represent the monoamine neurotransmitters, important regulators of behavior, movement, sleep, memory, and gut motility. SAME is an important cofactor in many chemical processes, including those involved in DA metabolism. Our hypothesis is that moderate to high blood phe may result in low brain levels of DA and 5-HT, and secondary abnormalities of SAME, which may associate with deficits in mental processes (i.e., memory and attention) in PKU patients. Dr. Gibson's experiments will examine the capacity

of these NPAAs to maximally restrict entry of phe into the brain of PKU mice, while minimally altering the entry of other LNAAs. Successful outcomes in these experiments may well lead to a totally novel therapy for PKU.



Genetic Metabolic Dietitians International (GMDI) research project will work to improve nutrition outcome in PKU. GMDI is a nonprofit organization for dietitians and other professionals who work with infants, children and adults with PKU and other inborn errors of metabolism. The funds from NPKUA will help develop national standards for nutrition management of PKU. GMDI is working with researchers at Emory University on this project. There are three goals of this project. First, is writing a paper for a professional journal to update nutrition management recommendations for PKU. This paper will be published in conjunction with medical management guidelines that are being written by a group of metabolic physicians. The goal is to have these two papers published this summer. Secondly, GMDI is working on a more extensive set of guidelines that will be specifically written for dietitians. This web-based document will include many details about PKU diet treatment that will be helpful for dietitians. Third, the funds will be used to develop a "tool-kit" that will include new and existing patient-friendly resources regarding the PKU diet for different age groups, including pregnancy.

NPKUA Research Selection Process

The overall funding strategy of the NPKUA is to support projects that will promote advances in the treatment and management of PKU, with a long-term goal of facilitating the development of a cure and to facilitate the growth and expansion of young, innovative researchers working in the inherited metabolic disease field. The NPKUA's Scientific Advisory Board is made up of eminently qualified physicians, researchers, and clinicians who are leaders in their fields to evaluate proposals, including Thomas Franklin, PhD; Harvey Levy, MD; Kathryn Moseley, MS, RD; Ray Stevens, PhD; Bryan Hainline, MD, PhD; and Uta Lichter-Konecki, MD, PhD.; Cary Harding, MD, FACMG; Desiree White, PhD; Jessica Cohen, MD; Dr. Francjan J. van Spronsen, MD, PhD. Each year this board goes through a rigorous evaluation process to select those proposals that will meet the above funding strategy.