



National  
**PKU**  
Alliance

## RESEARCH UPDATE



The 2014 Research Awards are named in memory of Sharon Johnstone, co-founder of the Mid Atlantic Connection for PKU and Allied Disorders. Sharon worked tirelessly to support loved ones with PKU and led the effort to raise more than a million dollars to find a cure. Her legacy is a cornerstone of the NPKUA's research strategy to support projects that 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.



**Dr. Kristen Skvorak** at the University of Pittsburgh Medical Center, has been pursuing groundbreaking experiments in liver cell transplants for PKU in a mouse model as a previous NPKUA Fellow. Since liver cells in PKU patients are deficient in PAH, this line of research involves replacing some of the defective cells with cells that have normal PAH activity.

Through this technique, part of the PKU-affected PKU liver is replenished with new cells from a donor or through stem cells. Dr. Skvorak's research has showed initial success with significant reduction in PHE levels and accelerated the first human hepatocyte transplant in the United States at UPMC in 2013. Kristen will continue to research in the PKU mouse model with hepatocytes, but will also begin investigations of alternate sources of cells for transplant, in particular human amnion epithelial cells (hAE).



**Dr. Eddy van derZee** is the Chair of Molecular Neurobiology at the University of Groningen, Netherlands. Dr. van der Zee will study the liberalization of dietary restrictions in PKU using LNAA supplementation in PKU mice. The association between elevated blood PHE concentrations and cognitive dysfunction in untreated PKU is well-known. However, the underlying mechanisms by which increased blood PHE levels lead to cognitive dysfunction have not been fully understood. Probably, the transport of phenylalanine from blood to brain plays a central role. PHE has been shown to be primarily transported from blood to brain by a particular transporter that also facilitates transport of other large neutral amino acids (LNAA). It has been suggested that high blood PHE concentrations strongly increase transport of PHE from blood to brain, while outcompeting the transport of other LNAA. In consequence, high brain phenylalanine concentrations and/or reduced brain concentrations of other LNAA would induce brain dysfunction in untreated PKU. As a possible new treatment for PKU, supplementation of LNAA other than phenylalanine aims to restore the disturbed amino acid transport from blood to brain. This could be accomplished by inhibiting the transport of phenylalanine, while stimulating the transport of other LNAA. The current research project will investigate the effects of different LNAA treatment regimens on the brain in a PKU mouse model. In the future, such LNAA treatment may liberalize the dietary restrictions for PKU patients.

The NPKUA's Scientific Advisory Board is made up of eminently qualified physicians, researchers, and clinicians who are leaders in their fields to evaluate the proposals the NPKUA receives each year.

Members include: 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; 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.

# 2014 Research Awards



**Dr. Michael Allen**, Associate Professor in the Dept. of Forensic and Investigative Genetics at the University of North Texas Health Science Center will look at the effect of PKU on the gut microbiome and its implications for probiotic therapy. Humans harbor a complex assemblage of microorganisms

within their intestines referred to as the “microbiome”. The gut microbiome consists of hundreds of species. The exact community composition is influenced by diet, drugs, environmental exposures, and host genetics. Elucidating the complex interactions between the microbiome and host has recently been an active area of research. Results indicate that the microbiome not only assists in digestion, but also influences development and immunity. The function of the microbiome is intricately linked to the host’s metabolism where it directly influences the circulating metabolic profiles of the blood. Dr. Allen’s research into the gut microbiome of a mouse-model of PKU fed a standard diet revealed the presence of a group of bacteria not found in wild-type mice. They hypothesize that these bacteria are specifically using phenylalanine and its metabolites from the host. If so, these bacteria might exert a protective effect by degrading PHE in the intestine and buffering its concentration in the blood. Application of such bacteria as probiotics could protect against excess PHE in the diet, and possibly enable easing of dietary restrictions.

Whereas white matter is implicated primarily in the transfer of information, gray matter regions are where the processing of the information occurs. Dr. Christ applies 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 received continued support to develop 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, 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. Shawn Christ** is Associate Professor of Psychological Sciences and Associate Director of the Brain Imaging Center at the University of Missouri, received a renewal grant to continue to 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.