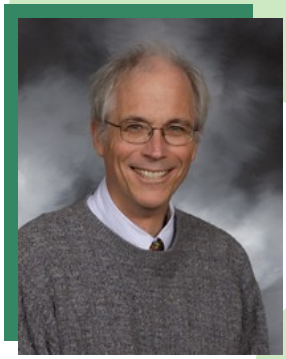
National PKU Alliance

2012 RESEARCH AWARDS

The National PKU Alliance is proud to announce its 2012 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. Cary Harding, Associate Professor of Molecular and Medical Genetics at Oregon Health & Science University in Portland, Oregon, has received a renewal research grant to continue his work on gene therapy to cure PKU in the PAH mouse models. He has focused on this research for more than 10 years with support from NIH. In order to translate this research into the clinic, vectors carrying the human PAH eDNA are being designed and carefully evaluated in a preclinical study. Specific gene therapy methods will be incorporated to improve the liver PAH expression from the human PAH eDNA and will be compared head-to-head in a short 8-week trial in PAH mice following portal vein injections and measuring the blood Phe levels. A second specific aim is to use sequences from the human 285 ribosomal RNA gene (rONA) in an effort to get permanent integration with the recipient genome so PAH expression will not diminish over time and thus could lead to a cure for PKU in humans.



Dr. K. Michael Gibson's research will focus on a new 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 *S*-adenosylmethionine (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.

Research Grants

Dr. Hunt von Herbing, Associate Professor in Department of Biological Sciences, University of North Texas, Denton, Texas & **Katherine Deming,** MS, Ph.D. Candidate and Project Leader will begin an 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, in order 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.

Postdoctoral Fellowships

Dr. Kristen Skvorak-Vallieu received a renewal postdoctoral fellowship to continue working at the University of Pittsburgh on her project entitled, "Hepatocyte and Induced Pluripotent Stem (IPS) Cell Transplants to Correct Phenlyketonuria". She is focusing on two hypotheses. The first hypothesis is that repopulation of the liver of PAH-deficient recipient mice with PAH proficient IPS derived hepatocytes will result in long-term correction of hyperphenylalaninemia. The second hypothesis is to test that PAH deficiency leads to alternations in bran catecholamine and monoamine levels which result in the chronic CNS damage of the disease. The NPKUA Scientific Advisory Board observed that the lab has very well-trained, experienced team working on this arena that could in fact result in a cure.

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; Emil Kakkis, MD, PhD; Harvey Levy, MD; Kathryn Mosely, MS, RD; Ray Stevens, PhD; Bryan Hainline, MD, PhD; and Uta Lichter-Konecki, MD, PhD. Each year this board goes through a rigorous evaluation process to select those proposals that will meet the above funding strategy.

National PKU Alliance
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