The National PKU Alliance is pleased to announce its 2019 Research and Post-Doctoral Fellowship Awards

These awards are made possible by our member organizations, Lifting the Limits for PKU national events and individuals 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.

Advancing Drug Development

Dr. Desirée White at Washington University in St. Louis, will validate cognitive tests that can be used to evaluate new treatments for PKU. Although advances have been made in treatment, most people with PKU find current treatments inadequate and believe new ones are needed. Until recently the development of new treatments, both pharmaceutical and dietary, have focused primarily on lowering blood Phe. However, even patients who maintain lower blood Phe can experience cognitive challenges. As such, cognitive tests are needed to show that new treatments improve cognition and therefore improve the daily lives of people with PKU. In her research, Dr. White will determine the utility of the National Institutes of Health Toolbox for this purpose. The Toolbox was chosen because it assesses key areas of cognition, such as executive abilities and attention, and is ideal for use across different clinical and research settings. Validation of the Toolbox will be a significant step in advancing the approval of new treatments.

New Pathways

Dr. Robbert Havekes at the University of Groningen, Netherlands, is exploring new pathways that regulate cell size and shape, and how these pathways are affected in PKU. Cell size and shape are critical in the proper functioning of cells and particularly important in maintaining proper connections within the central nervous system. Many PKU patients suffer from a number of cognitive and behavioral challenges. Understanding the role of cell size and shape in the underlying cause of these cognitive and behavioral challenges may lead to the development of new therapeutics that will improve the lives of PKU patients.
Cell-Based Therapy

**Dr. Roberto Gramignoli** at the Karolinska Institutet in Stockholm, Sweden, has been on the front line to the translation of cell-based therapies for liver diseases from the bench to the clinic. His group performed clinical liver cell transplantations first in the U.S. (at Children’s Hospital in Pittsburgh), and now in Scandinavian Countries. Liver cells are the preferred site to correct PAH genetic mutations. However, technical issues related to transplantation and required immunosuppression present practical limitations to broad use. These challenges encourage the search for alternative treatments such as placenta stem cells.

During the last decade, Dr. Gramignoli and his group have identified and reported the stem cell nature of human amnion epithelial (AE) cells isolated from term placenta. With support from the NPKUA, they have collected preclinical evidence on a new therapy for PKU and three additional life-threatening metabolic diseases. They received ethical approval to treat up to 10 patients with liver diseases at Karolinska and are in the process of creating the first AE cell bank worldwide, to generate cells potentially available “off the shelf” in every major medical center worldwide. Conversely to the current cell-based treatments, they have identified four different mechanisms supporting transplantation of allogenic AE cells. Although not the patient’s own cells, AE cells proved to be viable for transplant without taking immunosuppressive drugs. This may produce a fundamental change in the approach in cell transplantation, where the risk of side effects of immunosuppression is removed. One of the important objectives of Dr. Gramignoli’s 2019 project is to build a collection of donor cells to support a clinical trial beginning in late 2019 or early 2020.

Gene Therapy

**Dr. Cary O. Harding** at the Oregon Health & Science University continues to research gene therapy as a promising approach to treat PKU. His laboratory has successfully used novel adeno-associated virus (AAV) vectors to add a copy of the normal PAH gene into livers of PKU mice. This treatment restores the liver activity of the missing phenylalanine hydroxylase (PAH) enzyme and lowers blood Phe in PKU mice. However, he has found that the treatment is only temporary. CRISPR-Cas9 gene editing is a new technology that is capable of permanently correcting mutations in a disease gene. For this project, Dr. Harding and his team have designed and tested the necessary reagents to correct the PKU-causing mutation in PKU mice. Over the past year, Dr. Harding’s laboratory has experienced a significant breakthrough in the application of CRISPR in the PKU mouse models by achieving partial correction of blood Phe levels in CRISPR treated PKU mice. These results were presented at the American Society for Gene and Cell Therapy and NPKUA meetings, and NPKUA-sponsored Lifting the Limits fundraising events. The goal for this project in the next year is to improve the efficiency of this treatment and to achieve complete correction of blood Phe.

The overall funding strategy of the NPKUA is to support projects that will promote advances in the treatment and management of PKU with the long term goal of facilitating the development of a cure.
**How PKU May Affect The Brain**

**Dr. Shawn Christ**, Director of the Brain Imaging Center at the University of Missouri, studies how PKU may affect the brain. In the past, a lot of attention was focused on the potential effects of PKU on white matter connections of the brain. Recent research from his laboratory and others, however, suggest that gray matter structures of the brain (cortical, subcortical, and cerebellar) may also be affected in PKU. The present study is designed to continue this line of research and explore the relationship between the gray matter findings and markers of treatment adherence (plasma Phe levels), effects on brain white matter, and neuropsychological performance in a large sample of individuals with PKU. This year Dr. Christ is extending his studies to compare gray matter structure in PKU and non-PKU patients. The data from these studies will be used to support an application to the National Institutes of Health for a larger study to further expand the understanding of the relationship of blood Phe levels with structural changes in the brain. In addition to advancing the understanding of PKU and the brain, the project will hopefully serve as a stepping stone towards the establishment of an open-access repository for PKU neuroimaging data that can be used by researchers worldwide to share data.

**Styve Family Fellowship**

**Dr. Erik Koppes** is a Post-Doctoral Research Fellow in the Division of Medical Genetics at the Children’s Hospital of Pittsburgh of UPMC, working under the guidance of Dr. Robert Nicholls and Dr. Jerry Vockley. He is the recipient of the Styve Family Fellowship to develop, characterize and assess new model systems for understanding and treating PKU. His first goal is to validate a new preclinical pig model of PKU. He will continue to characterize the molecular features of the founding PKU pigs, work with the veterinarian team at the University of Pittsburgh to breed experimental cohorts of the animals, assess the effect of a low Phe diet in PKU pigs, and set up neurocognitive and behavioral tests. As a complementary component of his research, he will establish new technologies to better evaluate and correct phenylalanine hydroxylase (PAH) activity in PKU pig and human patient skin cells in culture.

**Post-Doctoral Fellowship**

**Dr. Jiping Yue**, University of Chicago Biological Sciences Division, has proposed a novel therapeutic strategy on PKU treatment by adapting a skin system to metabolize Phe. Its basic idea is based on the fact that skin is efficiently exposed to circulating Phe due to its blood supply. Therefore, the skin may function as a reaction tank to digest Phe from the bloodstream. For such purposes, skin grafts expressing Phe digesting enzyme will be grafted on PKU mice for treatment tests. It is expected that the grafts on PKU mice will continue to digest Phe and consequently lower blood Phe levels. Dr. Yue has successfully applied the similar theoretical settings to obesity and diabetes treatments. The preliminary data from his proposal have proved that Phe digesting enzyme functioned efficiently in skin grafts. His future study will focus on the establishment of the proposed engineered skin graft system and the evaluation of its Phe elimination efficiency on a PKU animal model.
The NPKUA’s mission is to improve the lives of individuals with PKU and pursue a cure.

Scientific Advisory Board

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: Cary O. Harding, MD, FACMG; Jessica Cohen, MD; Thomas Franklin, PhD; Ira J. Fox, MD; Rodney Howell, MD; Bryan Hainline, MD, PhD; Harvey Levy, MD; Uta Lichter-Konecki, MD, PhD; Kathryn Moseley, MS, RD; Erin MacLeod, PhD, RD, LD; Denise M. Ney, PhD, RD; Christineh N. Sarkissian, PhD; Ray Stevens, PhD; Francjan J. van Spronsen, MD, PhD; and Desiree White, PhD

Each year this board goes through a rigorous evaluation process to select those proposals that will improve treatment options and accelerate the timeline for a cure.