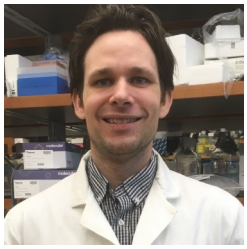
National PKU Alliance

2018 RESEARCH UPDATE

The National PKU Alliance is pleased to announce its 2018 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.

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 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.

How PKU May Effect 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 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. 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.

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 blood-stream. 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.

Research Renewals

Dr. Eileen K. Jaffe, Fox Chase Cancer Center, is studying how structure changes in phenylalanine hydroxylase (PAH) ensure the control of Phe concentration. PAH can respond to changing Phe levels by transitioning between different structures. Normal PAH turns itself "on" in response to rising Phe levels. PKU can be caused by PAH forms that are properly folded but cannot turn-on at appropriate Phe levels. The Jaffe lab is focused on developing ways to repair these dysfunctional enzymes as a therapeutic approach. The National PKU Alliance is supporting this work, which uses molecular biology, biochemistry, and X-ray crystallography. Having established the structure of turned-off PAH from a rodent, they are refining the human structure. The current focus is determining the structure of turned-on PAH using successfully designed PAH variants that are always turned-on. These studies promote the design of pharmacological chaperones that selectively stabilize turned-on PAH and restore a normal Phe response.

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 the mice. However, he has found that the treatment is only temporary. CRISPR-Cas9 gene editing is a very 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. Early results demonstrate partial but long-lasting correction of blood Phe levels in the mice. 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. Dr. Harding is very excited to evaluate this new technology as a potential treatment for PKU and other metabolic diseases.

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.

Tognarelli Family Fellowship

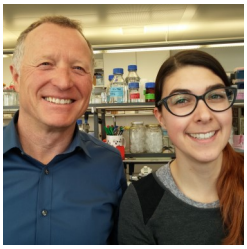
Dr. Katherine Durrer at the University of North Texas Health Science Center originally studied the use of a rodent bacterium and an antibiotic resistance gene. While useful for laboratory experiments, the strain was not considered safe for human use. She has now engineered a human probiotic to carry phenylalanine ammonia lyase (PAL). It is more stable and lacks antibiotic resistance, making it safer and more appropriate for human clinical trials. Tests in non-animal cultures indicate this new version metabolizes Phe very well. The Allen Lab at UNTHSC is working with Trayer Biotherapeutics to produce a clinically safe batch of this new probiotic to use in completing preclinical animal studies for Orphan Drug status, and any remaining preclinical animal studies for the Food and Drug Administration. Although there is no set path or timeline for a drug like this, she and her team hope to move into clinical trials by early to mid 2019.

Cell-Based Therapies

Dr. Roberto Gramignoli, Karolinska Institutet in Stockholm, Sweden, has been in 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. To correct metabolic defects as PKU, mature hepatocytes have been the elective choice, but the limited availability of cells for clinical approaches, in addition to the immunosuppressant regiment required to sustain the cell life-long, encourages the study of alternative treatments.

During the last decade, his group identified and reported the stem cell nature of human amnion epithelial (AE) cells isolated from term placenta. With support from the National PKU Alliance, 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.

New Research



Beat Thöny, Ph.D., Professor of Clinical Biochemistry at the University of Zürich and Head of Research in the Metabolic Division, is involved in the biochemical and genetic diagnosis of PKU and neurotransmitter disorders. Nicole Rimann has a Masters of Human Biology from the University of Zürich and is the research assistant for Dr. Thöny. The National PKU Alliance is supporting their ongoing research project towards a novel dietary treatment of PKU by gastrointestinal degradation of Phe to lower blood Phe levels in PKU subjects using an engineered probiotic. Probiotics are microorganisms that are considered to be safe and provide health benefits when consumed. They are using engineered Lactococcus lactis (L. lactis) that express recombinant phenylalanine ammonium lyase (PAL), an enzyme that converts Phe into harmless metabolites (trans-cinnamic acid and ammonia that are cleared in the intestine) and does not require a cofactor. Current versions of PAL-expressing strains still have safety and efficacy limitation for use in humans. They propose to evaluate new strains of recombinant L. lactis with improved safety and efficacy features critical for use in humans. Following successful completion of the proposed studies, they want to translate this strategy (with an industrial partner) to clinical trials and to eventually develop a new treatment or complementary treatment for PKU.

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

National PKU Alliance

The NPKUA's mission is to improve the lives of individuals with PKU and pursue a cure.

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