Dr. Eileen K. Jaffee, Fox Chase Cancer Center, is studying how structure changes in the phenylalanine hydroxylase enzyme (PAH) ensure the control of phenylalanine (Phe) concentration. Human 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 forms of PAH 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 long-term goal is to develop pharmacological chaperones that selectively stabilize turned-on PAH and restore a normal Phe response.

Dr. Robert Nicholls is Professor of Pediatrics in the Division of Medical Genetics at Children’s Hospital of Pittsburgh of UPMC and the University of Pittsburgh. Last year, NPKUA funding created the first PKU pig animal model using genome editing. This year Dr. Nicholls and his colleagues will breed pigs that are genetic PKU carriers and ones that have PKU to establish breeding stock and obtain sufficient offspring for experimental and control groups of animals for in depth studies. The pig model of PKU is characterized by growth retardation and hypopigmentation, and further clinical neurological, behavioral, and neuropathology studies will take place. This mini-pig model of PKU will provide a better understanding of the biomedical basis and allow for testing of new therapies for PKU.

Dr. Susan Waisbren, Senior Psychologist at Boston Children’s Hospital, will use new techniques to potentially close one of the most important gaps in the knowledge of PKU, namely to define how PKU affects the brain. This project will use an improved method for measuring brain Phe and tyrosine called two-dimensional shift correlated magnetic resonance spectroscopy (COSY). COSY is a non-invasive method that allows for quantitative measurement of Phe, tyrosine and other amino acids in the brain. The study will examine brain Phe and tyrosine in individuals with PKU and determine the association of Phe and tyrosine in distinct brain regions with measures of neuropsychological functioning and mood. COSY has the potential to explain individual differences in PKU, identify specific cognitive functions or mood disturbances related to high brain Phe or low brain Tyr, and offer an additional marker or endpoint for evaluating new treatments in clinical trials.

Dr. Dong Yizhou is Assistant Professor at Ohio State University. Dr. Yizhou hypothesizes that gene corrections to PAH will produce a functional PAH protein and recover the metabolic process, resulting in a cure for PKU. In this study, he will develop a gene-engineering platform in order to induce gene editing as well as correct the mutations of the PAH gene. This strategy would provide a new avenue for the treatment of PKU and such strategies could potentially be applied to other therapeutic applications.
Dr. Roberto Gramignoli at the Karolinska Institutet in Stockholm, Sweden has been focused in cell-based therapies to correct metabolic defects. His group performed clinical hepatocyte transplantations first in the US (at Children’s Hospital in Pittsburgh), and now in Sweden. Simultaneously, they identified and reported the stem cell nature of the amnion epithelial (AE) cells isolated from term human placenta. Thanks to previous NPKUA support, they collected preclinical evidence on a new therapy for PKU and three additional life-threatening metabolic diseases, including the most detailed study and correction ever reported by a human stem cell. Dr. Gramignoli received ethical approval to treat up to 10 patients with liver diseases at Karolinska. He now has scientific data supporting that AE cells can be transplanted without immunosuppressive therapy in support. This will produce a paradigm shift in cell transplantation, where the risk of side effects of immunosuppression is removed.

Dr. Francjan van Spronsen, Professor of Pediatrics at the University of Groningen, Netherlands, will focus on finding the difference towards personalized PKU treatment. Case reports show that some classical PKU patients escape from severe intellectual disability if not diagnosed/treated in their first years, possibly due to abnormal Phe transport from blood to brain. Dr. van Spronsen will collect material from late-diagnosed classical PKU patients with normal development, and will study Phe transport in their skin cells and look for differences in their DNA compared to late-diagnosed PKU patients with severe intellectual disability. Thereby, Dr. van Spronson and his research team hope to find the difference between patients in whom high blood Phe clearly is very dangerous and patients in whom high blood Phe clearly is less dangerous.

Dr. Cary O. Harding at the Oregon Health & Science University, continues to research gene therapy as a promising approach to cure PKU. His laboratory has had success using novel adeno-associated virus (AAV) vectors to add a copy of the normal PAH gene into livers of PKU mice. This treatment restores liver activity of the missing 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. In this project, he will design the necessary CRISPR-Cas9 reagents to directly correct the PAH gene in PKU mice. This should lead to long term restoration of liver PAH activity and normal blood Phe concentrations in treated mice. Dr. Harding is very excited to evaluate this new technology as a potential cure for PKU and other metabolic diseases.

Dr. Katherine Durrer-Deming at the University of North Texas Health Science Center is continuing her research into the ability of a genetically engineered probiotic to lower blood Phe levels in PKU mice. The creation of a human safe version of a genetically engineered probiotic to treat PKU is nearly complete. This human version is a Lactobacillus strain engineered to carry a Phenylalanine Ammonia Lyase (PAL) gene. PAL enzyme activity has been verified in cell culture extracts. To confirm efficacy and safety, a large group of mice will be fed the treatment probiotic for several months. Animals will be monitored for up to three months post treatment to determine potential long term residency in the gut. The data generated from these experiments will assist in working towards FDA approval for human clinical trials.

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; 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.