To date, NPKUA has provided nearly $6 million to fund over 80 grant projects. See some of the approved grant projects from the last few years:

2024 Grant Season

- **Cell Therapy for Phenylketonuria**
  Markus Grompe, M.D., Oregon Health & Science University

  Dr. Grompe and his team are working on a new treatment for PKU. Their research started in 2021 and focuses on using the hepatocyte liver cells for cell therapy. These cells are designed to avoid being attacked by the immune system so that they can be transplanted from one person to another. To optimize the growth of the transplanted cells, this team has altered these liver cells so that they can survive and grow when exposed to acetaminophen, that can kill liver cells in high doses. In tests with mice that have PKU, this method has successfully lowered phenylalanine (Phe) levels in the blood for extended periods of time.

  Next, the researchers will work on creating human liver cells that can hide from the immune system and won't be rejected after transplantation. If this works, they will test these cells in mice with PKU and later move on to testing in larger animals with more advanced immune systems.

- **Novel Approaches to Achieving Permanent Gene Correction in PAH-Deficient Mice**
  Cary Harding, M.D., Oregon Health & Science University

  Dr. Harding and his team have been working on this project since 2018 to develop a safe and lasting cure for PKU using gene editing focused on the liver. In this project, they are testing a method that uses CRISPR/Cas9 technology to insert a new gene into the livers of mice with PKU. This gene produces phenylalanine hydroxylase (PAH), the defective enzyme in people with PKU. If the gene insertion works, the team will use a special technique involving acetaminophen to allow the edited liver cells to grow preferentially over the unedited cells. The goal is to increase concentrations of these cells in the liver to allow for enough phenylalanine hydroxylase enzyme to metabolize Phe and lower blood Phe levels in the PKU mice.

- **The Burden of PKU on both the disease and its treatments: Asking the right questions toward the first PKU-PROEM**
  Francjan van Spronsen, M.D., Ph.D., University of Groningen

  Dr. van Spronsen and his team are creating and validating a new questionnaire to understand the full impact of living with PKU. This tool will be used worldwide and will include questions about both how PKU affects daily life and how treatments impact patients. To make the questionnaire, they will gather the right words and phrases to describe these experiences. This will then be used to develop a validated Patient Reported Outcome and Experience Measure (PROEM) questionnaire that will assess the full burden of PKU on daily life. Dr. van Spronsen has already brought together healthcare providers, researchers, and patient advocacy groups from around the world to help create this tool.

2023 Grant Season

- **Development of Novel Psychological Assessment Tools & Anxiety Intervention for PKU**
  Shawn E. Christ, Ph.D., University of Missouri

  The focus of this research is to explore the efficacy and feasibility of a short-term skills-based intervention (Show ME FIRST) on anxiety and depression in adolescents with PKU. Additionally, this team plans to assess the validity of a novel assessment tool created by their research team to capture real time neurocognitive and psychological function.

- **Cell Therapy for Phenylketonuria**
  Markus Grompe, M.D., Oregon Health & Sciences University

  This research is a continuation of Dr. Grompe's grant project starting in 2021. This ongoing project explores the methods of overcoming two current challenges with hepatocyte transplantation as a cure for PKU: insufficient cell replacement levels to achieve correction of systemic phenylalanine levels, and issues related to immunosuppression. To combat insufficient cell replacement levels, their team has developed a system of cell expansion via gene-edited liver cells, hepatocytes, that are resistant to the drug acetaminophen. These gene-edited hepatocytes will preferentially expand over the non-gene edited cells that are not resistant to acetaminophen toxicity. This approach has proven to provide long-lasting therapeutic correction of blood phenylalanine levels in a PKU mouse model. Secondly, their team plans to generate immune stealthy hepatocytes to prevent immune rejection in allogenic hepatocyte transplantation.

- **Structural Insights into the Regulation of Phenylalanine Hydroxylase in Phenylketonuria**
  Kushol Gupta, Ph.D., University of Pennsylvania

  This research aims to gain a detailed mechanistic understanding of the regulation of the PAH enzyme by creating a synthetic version of two *PAH* gene mutations that can rescue the mutated PAH enzyme increasing its enzymatic activity. They hope this will allow for a determination of the molecular basis of allosteric regulation of the PAH enzyme and a better understanding of how clinical mutations affect PAH enzyme regulation. This approach can potentially lead to development of future treatments for PKU.

- **Novel Approaches to Achieving Permanent Gene Correction in PAH-Deficient Mice**
  Cary O. Harding, M.D., Oregon Health & Sciences University

  This research is part of an ongoing project from Dr. Harding since 2018. His work aims to investigate the therapeutic effectiveness of two possible approaches in a PAH-deficient mouse model of human PKU: CRISPR-Cas9 facilitated gene integration of a phenylalanine *hydroxylase (PAH)* gene into the hepatocyte genome of PAH-deficient mice, or a novel gene editing strategy called Programmable Addition via Site-specific Targeting Elements (PASTE) that could improve the frequency of gene editing.

- **Can Care of Adult PKU Be Improved with Additional Dietary Large Neutral Amino Acids: A Protocol for an Nof-1 Study**
  Shoji Yano, M.D., Ph.D., University of Southern California

  This research will use Phenylalanine (Phe), Tyrosine (Tyr), and the Phe/Tyr ratio as biomarkers, as well as other clinical assessments to determine the impact of large neutral amino acids (LNAAs) on the outcomes of PKU adults. LNAAs have historically been used as a treatment to reduce the amount of Phe that can be taken up by the brain through competition with other neutral amino acids across the LATI transporter. Their team hopes to identify the appropriate use of LNAAs to improve neurocognitive symptoms and possibly allow increased dietary protein intake. This study was previously awarded grant funding from the NPKUA but has requested additional funds to increase enrollment in hopes of providing more definitive study results.

2022 Grant Season

- **Cell Therapy of Phenylketonuria**
  Markus Grompe, M.D., Oregon Health & Sciences University

  The research to be conducted will explore methods of overcoming two current challenges with hepatocyte transplantation as a cure for PKU: insufficient cell replacement levels to achieve correction of systemic phenylalanine levels, and issues related to immunosuppression. To combat insufficient cell replacement levels, their team has developed a system of cell expansion via gene-edited hepatocytes that are resistant to the hepatotoxic effects of the drug acetaminophen. These gene-edited hepatocytes will preferentially expand over the non-gene edited cells that are not resistant to acetaminophen toxicity. This approach has proven to provide long-lasting therapeutic correction of blood phenylalanine levels in a PKU mouse model. Secondly, their team plans to generate immune stealthy hepatocytes to prevent immune rejection in allogenic hepatocyte transplantation.

- **Novel Approaches to Achieving Permanent Gene Correction in PAH-Deficient Mice**
  Cary Harding, M.D., Oregon Health & Sciences University

  This project aims to investigate the therapeutic effectiveness of two possible approaches in a PAH-deficient mouse model of human PKU: CRISPR-Cas9 facilitated gene integration of a phenylalanine *hydroxylase (PAH)* gene into the hepatocyte genome of PAH-deficient mice, or a novel gene editing strategy called Programmable Addition via Site-specific Targeting Elements (PASTE) that could improve the frequency of gene editing.

- **Identification of linguistic markers revealing severity of symptom in phenylketonuria: A novel measurement tool for clinical trials**
  Susan Waisbren, Ph.D., Boston Children's Hospital

  This research explored the effectiveness of the Cookie Theft Picture Task, which is a standardized instrument used to quantify parameters of spontaneous speech. Dr. Waisbren and her team are interested to understand if this tool could be used to measure the subtle deficits associated with neurocognitive functioning in individuals with PKU. If proven effective, the Cookie Theft Picture Task could be used to capture the benefits of developing treatments.

2021 Grant Season

- **Intervention Targeting PKU Cerebral Energy Deficit and Oxidative Stress**
  Steven F. Dobrowolski, Ph.D., University of Pittsburgh School of Medicine

- **Cell Therapy for Phenylketonuria**
  Markus Grompe, M.D., Oregon Health & Sciences University

- **Novel Approaches to Achieving Permanent Gene Correction in PAH-Deficient Mice**
  Cary Harding, M.D., Oregon Health & Sciences University

- **Understanding the Molecular Basis for Hyperphenylalanemia Toxicity and Developing Therapeutic Options for PKU Patients**
  Erik Koppes, Ph.D., Children's Hospital of Pittsburgh

- **Can Care of Adult PKU Be Improved with Additional Dietary Large Neutral Amino Acids-an N-of-1 Study**
  Shoji Yano, M.D., Ph.D., University of Southern California, Keck School of Medicine

2020 Grant Season

- **Generation of the First Placenta Stem Cell Bank for Phenylketonuria Treatment**
  Roberto Gramignoli, Ph.D., Karolinska Institutet

- **Novel Approaches to Achieving Permanent Gene Correction in PAH-Deficient Mice**
  Cary Harding, M.D., Oregon Health & Sciences University

- **Understanding the Molecular Basis for Hyperphenylalanemia Toxicity and Developing Therapeutic Options for PKU Patients**
  Erik Koppes, Ph.D., Children's Hospital of Pittsburgh

- **Validation of the NIH Toolbox for Use in Phenylketonuria Clinical Trials**
  Desiree White, Ph.D., The Washington University

- **Curing Hyperphenylalaninemia by Engineering Tractable Native Bacteria**
  Amir Zarrinpar, M.D., Ph.D., The University of California, San Diego

2019 Grant Season

- **Metabolic, Behavioral, and Neurologic Correlates of Gray Matter Abnormalities in Individuals with Early-Treated PKU**
  Shawn E. Christ, Ph.D., University of Missouri

- **Generation of the First Placenta Stem Cell Bank for Phenylketonuria Treatment**
  Robert Gramignoli, Ph.D., Karolinska Institutet

- **Novel Approaches to Achieving Permanent Gene Correction in PAH-Deficient Mice**
  Cary Harding, M.D., Oregon Health & Sciences University

- **A Novel Approach to Combat Cognitive Deficits Associated with PKU: The Role of the Protein Cofilin, a Key Player in Synaptic Plasticity**
  Robbert Havekes, Ph.D.

- **Validation of the NIH Toolbox for Use in Phenylketonuria Clinical Trials**
  Desiree White, Ph.D., The Washington University

- **Development of Epidermal Progenitor Cell-based Therapy of Phenylketonuria**
  Jiping Yue, Ph.D., University of Chicago