



*A 2010 NPKUA Funded Research Project*

**RESEARCH GRANT SUMMARY**  
**“CELL TRANSPLANTATION FOR PHENYLKETONURIA”**

*Dr. Roberto Gramignoli, Department of Pathology, University of Pittsburgh School of Medicine*

Can cell transplantation help individuals with PKU? Dr. Roberto Gramignoli will study this question using “hepatocyte (liver cell) transplantation” (HTX) in the liver, which has been shown to successfully treat other metabolic disorders.

PKU is one of the most common metabolic disorders. Individuals with PKU are deficient in the enzyme, phenylalanine hydroxylase (PAH), needed to metabolize phenylalanine (“phe”). Without PAH, phe accumulates and becomes toxic. Not following a restricted, lifelong diet low in phe can lead to brain damage and other problems for those with PKU

Even with an effective, lifelong diet, there is still an unmet need for alternative treatments for PKU, Gramignoli states. The importance of his study is that it could change the lives of those who have PKU. Gramignoli notes that it is common for individuals to quit the PKU diet in life because it is unpalatable and expensive. However, going off diet for those with PKU can lead to serious health risks, such as brain damage, memory issues, and seizures.

Studies have indicated that restoring as little as 5 to 10 percent of the PAH deficiency in the liver can correct elevated phe levels, which are what become toxic to those with PKU. PAH is manufactured in the liver and Dr. Gramignoli’s study seeks to determine if liver cell transplantation (HTX) can correct the deficiency in a PKU mouse. HTX has been shown to correct metabolic liver disease in many other animals and in patients with metabolic liver disease. If successful in the PKU mice, these studies will generate data to help those affected with PKU.

In his research, Dr. Gramignoli will repopulate the liver of PKU mice by transplanting PAH proficient hepatocytes. These normal liver cells will grow and regenerate in the recipient’s liver to restore the liver’s ability to make PAH. The PAH will then breakdown the phe and correct high phe levels in the blood in those with PKU, allowing them a less restricted diet.

Further, Gramignoli will study changes in brain chemistry after transplantation. Since PKU is associated with phenylalanine hydroxylase (PAH) deficiency, this deficiency leads to changes in brain chemistry, which can cause permanent brain damage. Gramignoli’s study proposes that following transplantation, brain chemistry will return to normal as phe levels in the blood normalize. The phe levels therefore would not become toxic.

It is expected that transplanting 5 to 10 percent of donor PAH-proficient cells in the liver will result in decreased phe in the blood in Gramignoli’s study. Normalization of phe levels will result in correction of brain imbalances of amino acids and neurotransmitters, and normal PAH activity will result in normal phe levels throughout the body.