

Propionic Acidemia Foundation News

Research Update:

The following progress has been made by Dr. Toru Miyazaki, M.D., Ph.D. and his research team during 2002 towards developing a gene therapy for PA patients.

Ultimately the goal is to transplant hepatic (liver) stem cells into the liver of a PA patient. Newborns or possibly even pre-term babies may be the first recipients of a future therapy, as cells carrying correct PCCA and PCCB genes can be injected into the umbilical vein that flows directly into the liver.

Stem cells injected into the umbilical vein of mice were successfully transplanted to the liver. Embryonic stem (ES) cells were injected into late stage mouse embryos. At 3-4 weeks of age, the livers of the mice were examined. A significant proportion of ES-derived cells was identified in the host liver, and the population of these cells was dependent on the initial injection. This indicates that a stem cell approach to deliver correct PCCA or PCCB genes is possible. Improving the injection method should achieve an even higher percentage of cells that are delivered and reproduce in the liver.

The process of differentiating ES cells to hepatocyte-committed stem cells *in vitro* has been initiated. Stem cells go through a process called "differentiation". This is basically a process by which they mature into different cell types. Transplantation of undifferentiated ES cells into a host is known to cause tumors. For this reason hepatocytes (liver stem cells) will be needed as donor cells. Once the correct conditions are established, ES cells in the lab should yield a population of hepatocytes suitable for transplantation studies.

A new strain of mice has been designed to allow an ON/OFF control of the PCC (propionyl CoA carboxylase) gene. Construction of the gene needed to create the mice is underway. This new mouse strain will be used to receive transplanted hepatocytes carrying correct PCCA/PCCB genes. After the inoculated cells have had time to become functionally mature in the liver, the PCC gene of the mouse can be turned "off" to test whether the transplanted hepatocytes are producing PCC. The mice will be followed to determine the efficacy of the transplantation therapy.

Donations sent to the Propionic Acidemia Foundation (PAF)/UT Southwestern Medical Center in 2002 have allowed Dr. Miyazaki to hire a new postdoctoral fellow to join his lab. In April, 2003 an M.D. of Pediatrics will

begin work on the PA project. In addition to the experiments above, he is planning to purify and enrich hepatic stem cells (to be used as donor cells) from mouse bone marrow cells using a cell sorting system at the Center for Immunology at UT Southwestern.

Financial Update:

Happy New Year. The PAF accomplished a lot during 2002. Our fundraising goal was \$65,000 and PA families were able to raise \$87,151 for Dr. Miyazaki's research at UT Southwestern Medical Center. Research is expensive and every dollar we raise counts. We have big plans for 2003!

The Propionic Acidemia Foundation is in process to become an Illinois corporation and will be applying for 501c3 status. This will enable us to expand our fundraising efforts and search for other researchers and a cure for PA. Our 2003 fundraising goal is \$100,000 and we need your help. Please check out the web-site at www.pafoundation.com and contact one of us if you can help out. — PAF Committee

Janice Boecker-512-892-1288/rnjboeck@texas.net

Jill Franks-847-579-1824/pafoundation@attbi.com

Ruth Milne-011-44-011224 316505/Oilfieldsales@aol.com

Susan Millette-207-283-

9654/milletts@midmaine.com

Kathy Stagni - 763-559-1797/OAANews@aol.com

The PAF thanks all the families and individuals who have given their time, talents and money to help promote this promising research! Anyone wanting additional information or further explanation of the studies may contact Janice Boecker at rnjboeck@Texas.net, 512-892-1288, or contact Dr. Miyazaki at toru.miyazaki@UTSouthwestern.edu.