

## **Non-technical Abstract**

As an early step to gene therapy for inherited metabolic diseases, we propose to transfer genes to the liver of patients suffering from a partial lack of ornithine transcarbamylase (OTC), an enzyme which helps clear ammonia from the bloodstream. This is accomplished by genetically engineering the OTC gene into an adenovirus, which is a virus common to humans which can cause respiratory and flu like symptoms. This recombinant adenovirus has been altered so that it is less likely to cause symptoms. The recombinant adenovirus acts as a "taxi" to deliver the OTC gene to the liver cells where ammonia is normally broken down. Once it enters the cell, the gene can produce a "blueprint" for the production of the normal OTC enzyme leading to the elimination of ammonia. In the laboratory, studies of this recombinant adenovirus have shown that it makes large amounts of OTC enzyme. When injected into the vein of a mouse born with OTC deficiency (exactly like the deficiency in patients), the current version of the engineered virus has shuttled the gene to the liver resulting in correction of the OTC deficiency for over one month. The OTC levels have increased from 10-15% to virtually 100% of normal in all liver cells. Before considering a similar therapeutic trial of recombinant adenoviral gene therapy for individuals with OTC deficiency, we need to identify the correct dose of virus to use. Like any medication, an ideal dose would be sufficient to correct the OTC deficiency but not so high as to cause significant side effects. The purpose of the current study is to test a series of gradually increasing doses of recombinant adenovirus in order to identify the amount to use in the subsequent gene therapy treatment study. We will be testing both men and women 18 years or older with normal intellectual function who have confirmed partial OTC deficiency. We will not include in this study individuals who have a history of liver disease (such as viral hepatitis) or cardiovascular disease (such as high blood pressure, angina or heart attacks), and we will exclude women who are pregnant or nursing, until we learn more about the possible transmission of the recombinant virus to the developing fetus. The major risks include: Recombinant adenovirus administration: - This study marks the first time recombinant adenoviruses have been placed in the blood stream for purposes of gene transfer. As such it is difficult to predict exactly how people will respond. In mice and monkeys high doses of the virus have been associated with evidence of liver inflammation (hepatitis), hepatic necrosis and death. To reduce this risk, we are starting at a very low dose of virus and introducing the virus into only part of the liver so that if significant damage occurs, it is likely it will only happen in one part of the liver. In the worst-case scenario, however, there is the possibility of a severe liver injury (hepatitis) requiring a liver transplantation or leading to death. The second aspect of risk to the recombinant adenovirus administration relates to the development of neutralizing antibodies against either the adenovirus or the OTC protein; Gene Transfer by angiography: - Angiography is a commonly used and generally safe procedure, however, there are often minor complications such as bruising and swelling at the site of injection. In addition, it may be necessary to perform more than one puncture to gain access to the blood vessel in the liver for the purposes of the study. Occasionally (incidence < 1%), serious complications of angiography occur. These include clotting of the groin artery leading to poor circulation of the leg, and rupture of the artery leading to internal bleeding. These complications would require surgery to correct. Other potential problems include clotting of the artery in the liver, or an allergic reaction to the X-ray dye used to confirm position of the catheter. These rare problems require treatment by drug or other medical therapy; Liver biopsy: - The most common complication of liver biopsy is bleeding from the puncture site. Occasionally (incidence < 1%) the bleeding is severe enough to require surgery to control. It is important to emphasize that this study is not likely to directly benefit patients, because we are using low doses of the virus which should not completely correct the OTC deficiency, but we believe the benefits of the knowledge gained by doing this study outweigh the potential risks to the individual patients.