Functional Analysis of Genetic Variants in ATP7B Discovered in a Patient with Neonatal Acute Liver Failure

What: We will investigate a role of genetic mutations in ATP7B in a severe liver failure of a newborn who required liver transplant.
Why: Finding the cause of newborn liver failure will provide specific treatment options and potentially spare a liver transplant. Also, making genetic diagnosis will affect medical care for the family's future children.
How: We will use human hepatocytes derived from induced pluripotent stem cells and edit their genome to test the effect of the mutation.

In pediatrics, etiology of acute liver failure is often indeterminate therefore no specific treatment is applicable leaving liver transplant as the only option. We have experienced 2 recent cases of neonatal acute liver failure that required a high-risk urgent liver transplantation to save the patient. In this study, we aim to investigate one of the cases retrospectively by using a novel in-vitro modeling technology to reveal the cause of the patients' neonatal acute liver failure. Identifying this cause will allow the possibility of medically treating patients with similar clinical presentation and avoid high-risk liver transplant operations.

For this case, a whole exome sequencing (WES) of the patients' genome was compared with that of their parents. The WES revealed rare variants in ATP7B gene, which encodes a protein responsible for copper metabolism. This defect can cause Wilson disease, a well-studied liver disease that causes copper accumulation in the liver which can lead to acute liver failure. Our goal is to dissect the pathogenic mechanisms of ATP7B mutations found in this patient using an experimental strategy that utilizes a human model system that is directly relevant to human biology and disease (Exhibit A). In our preliminary analysis, we found ATP7B is highly expressed at the final stage of hepatic development, suggesting an important role of ATP7B during the hepatocyte differentiation. Building on these results, we propose the overall hypothesis that our hepatocytes with ATP7B mutations of this patient show the pathogenic mechanisms of the patient's liver diseases during hepatic differentiation. This hypothesis will be tested by the experiments proposed in the following aim.

Specific Aim: To define the mechanisms of hepatocyte injury induced by ATP7B mutations
Hypothesis 1: ATP7B deficiency induces cellular injury during hepatocyte differentiation
Hypothesis 2: ATP7B mutations in hepatocytes exhibit the defect in the copper metabolism

Exhibit A.