2016 Million Dollar Bike Ride
Pilot Grant Program

**Application Title:** Exploring the postnatal requirement of the brain for the Glut1 protein

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Haploinsufficiency of the *SLC2A1* (Glucose Transporter 1) gene and reduced levels of its translated product, the Glucose Transporter 1 (Glut1) protein trigger the rare but severe pediatric neurodevelopmental disorder, Glut1 deficiency syndrome (Glut1 DS). Patients suffer a multitude of effects including epileptiform seizures, cognitive dysfunction, developmental delay, and movement disorders. It is unclear precisely how low Glut1 protein evolves into these particular disease characteristics; not surprisingly, there is no optimal treatment for Glut1 DS. Glut1 DS has been previously modeled in mice and we have used the mutants to explore the promise of a novel therapeutic strategy – gene replacement – for the human disease. We showed that early treatment is remarkably protective, mitigating every major aspect of the disease phenotype. Here we wish to expand on these findings. This will be pursued with two related goals in mind. First, we wish to investigate the therapeutic effects of restoring Glut1 late in the disease. Second, we will determine if the requirements for Glut1 change once adulthood is attained. Our collective experiments, which take advantage of model mice, are expected to inform the design of gene replacement-type therapies and set the stage for more mechanistic studies linking low Glut1 to the brain dysfunction characteristic of Glut1 DS.