Penn Medicine
Orphan Disease Center

CDKL5 Program of Excellence
Pilot Grant Program

Application Title: Pharmacological Reactivation of the Xi-Linked CDKL5 Gene as a Potential Treatment for CDKL5 Deficiency Disorder

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CDKL5 Deficiency Disorder is a rare disease that occurs primarily in females, and results in recurrent seizures that begin in infancy as well as a variety of severe developmental problems. The disease is caused by mutations in a gene called CDKL5, which makes a protein that is required for normal neuronal circuit function in the brain. The CDKL5 gene is located on the X chromosome. Females have two copies of the X chromosome in each cell, but one of the X chromosomes gets randomly inactivated (turned off) due to a normal and important biological process called X chromosome inactivation (or XCI). In females with CDKL5 Deficiency Disorder only one of the two copies of the CDKL5 gene is mutated and females therefore have a mixture of cells, some of which have the normal copy of CDKL5 “on” and the mutant copy “off”, and some of which have the mutant copy of CDKL5 “on” and the normal copy “off”-the latter are the disease-causing cells. One potential strategy for treating CDKL5 Deficiency Disorder is to switch back on the normal CDKL5 gene. As an initial step toward developing therapeutic drugs that can switch back on the normal CDKL5 gene, we first identified a number of proteins that are required for XCI (called XCI Factors or XCIFs)—these proteins are responsible for turning the normal copy of CDKL5 off. We then identified drugs that could bind to the XCIFs and block their function, causing the normal copy of CDKL5 to switch back on. Our current efforts are aimed at identifying new XCIFs and evaluating their suitability as targets for the development of drugs to treat CDKL5 Deficiency Disorder.