Penn Medicine
Orphan Disease Center

# CDKL5 Program of Excellence
# Pilot Grant Program

**Application Title:** Treating CDKL5 Syndrome by reactivating the silent allele of CDKL5

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**Institution:** Massachusetts General Hospital

Our goal is to unlock the inactive X chromosome to express the good copy of the CDKL5 gene to treat symptoms of the CDKL5 Syndrome. Our newly developed technology enables us to pharmacologically reactivate genes on the Xi (inactive X). With this technology, we have identified dozens of druggable proteins that collaborate with Xist RNA to shut down the Xi. Our goal is to reactivate the Xi by inhibiting these protein interactors. In preliminary work, we have now shown that targeting two or more factors simultaneously results in upregulation of select genes on the Xi. Here, our specific aims are to define drug combinations for *CDKL5* reactivation in patient cells, and test the efficacy and safety of these drug combinations in the mouse.