Penn Medicine
Orphan Disease Center

CDKL5 Program of Excellence
Pilot Grant Program

Application Title: Development of TALE and CRISPR/Cas9 as a putative therapy for treatment or correction of genetically linked CDKL5 Deficiency

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Our team focuses on genetically-linked pediatric neurological disorders such as CDKL5 that are caused by single gene mutations and are targetable with gene editing molecules. We are identifying areas in the DNA sequence using state of the art technology that we can target and synthetically modify. Our current research is focused on the therapeutic application of transcription activator-like effector (TALE) and clustered regularly interspaced short palindrome repeats (CRISPR) to modify gene expression in genetically-linked neurological diseases. We will use the known information of CDKL5 to guide our construction of potent, precise gene editing modalities. These platforms can turn on or enhance the gene, silence expression of the gene, cause permanent epigenetic changes, or remove a piece of DNA via targeted double stranded breaks essentially allowing for custom modifications to be made at the DNA level. We have identified 3 unique genomic regions that fit the criteria established in our lab. We have created CRISPR guide RNA for each of these regions that will be paired with a nuclease-deficient (will not cause DNA breakage) Cas9, paired with the transcriptional activator VP64 to turn on the healthy gene that is silenced in CDKL5 deficiency. We have also created a transcription activator-like effector paired with VP64 for the same genomic region. We are currently studying the efficacy of this approach using patient-derived CDKL5 cells.