



CDKL5 Program of Excellence 2019 Pilot Grant Program

Project Title: "Development of Targeted Frameshifting Technologies" (2018)

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Genome editing technologies have the potential to repair the mutations that cause genetic disease. Although a significant number of genetic diseases arise from the insertion or deletion of a small number of DNA base pairs that result in frameshift mutations within genes, current methods to correct small insertions or deletions are inefficient, are limited to cells that are actively dividing, and typically result in an excess of unwanted stochastic insertions or deletions at the target site that inactivate, rather than repair, the target gene or regulatory sequence. We have proposed the development of an entirely new class of genome editing technology that will enable the efficient site-specific correction of small insertion or deletion mutations, including mutations that can give rise to CDKL5 Deficiency Disorder (CDD). To achieve this goal, in our first year funded by the Loulou Foundation, we designed and characterized a targetable molecular machine capable of site-specifically install nucleotides within DNA in a test tube and developed a platform for its use in human cells. We now propose to further engineer and evolve our nucleotide insertase to enable it to insert individual nucleotides into genomic DNA at targeted sites, enabling the correction of different frameshift mutations that can cause CDD and numerous other genetic diseases.