THE HARTWELL FOUNDATION

2024 Nominee Individual Biomedical Research Award

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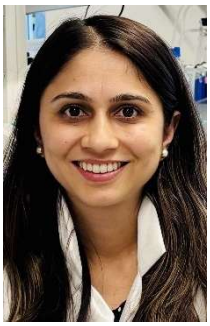

Precise Genome Editing to Correct DNA Mutations and Restore Gene Expression in Neurodegenerative Disease

Rare genetic disorders affect approximately 1 in 20 American children. One such example is Wolfram syndrome (WS), a rare, autosomal recessive neurodegenerative disease characterized by childhood onset diabetes, loss of vision and hearing, and progressive nervous system dysfunction. Nearly 5000 cases of WS currently exist in the US today, with the majority due pathogenic mutations in the Wolfram syndrome 1 gene (*WFS1*), which encodes an essential transmembrane protein located primarily in the endoplasmic reticulum called wolframin, which participates in the intracellular regulation of calcium ions and is expressed at highest levels in brain, pancreas, heart, and pancreatic beta cells. Many patients begin developing symptoms of WS around the age of six. The prognosis is currently poor, as there are limited therapeutic options with no definitive cure. Palliative strategies include small molecule drugs that reduce some of the symptoms, but there is no treatment available that can delay, halt, or reverse the progression of WS. Continual symptom progression and complications caused by neurodegeneration lead to eventual death of most patients by age 30. To address the need for life-saving treatment, I will seek to prevent neurodegeneration in WS by leveraging novel precision genome editing technology known as base editing, a cutting-edge genome editing technique that allows precise modifications of DNA without cutting it. In this way, I propose correcting the pathogenic mutation that causes Wolfram syndrome with a one-time permanent solution that will restore endogenous gene expression while preserving native WFS1 gene regulation; effectively addressing the root cause of the disease without risk of systemic genotoxicity. My strategy will be to identify and optimize base editor enzymes and sgRNA suited for correcting the WFS1 mutation. The optimal combination will achieve maximal editing efficiency while minimizing off-target effects, ensuring the safety and efficacy of the therapeutic approach. My 3-step plan is to deploy base editing strategies to correct WFS1 mutations in human cell lines, in vitro; evaluate therapeutic efficacy of base editing in patient-derived cells, in vitro; and evaluate therapeutic efficacy of base editing to protect against neurodegeneration in a mouse model of WS, in vivo. For gene therapy, I will use adeno-associated virus (AAV) as a delivery system, which has been approved by the FDA for use in treating other neurodegenerative diseases and has demonstrated favorable safety profiles in children. If I am successful in implementing a precise genome editing strategy for WS, it will also advance the technology for use against other rare genetic diseases, providing affected children for the first time with a therapeutic option and the potential for a cure.