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Precision Genome Editing for Treating Single-gene Disorders

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There are an estimated 6,000 human single-gene disorders, most of them have no cure. This imposes a significant burden on human health worldwide. The recent advent in developing engineered nucleases, especially CRISPR/Cas9 (clustered, regularly interspaced, short palindromic repeats and CRISPR-associated protein 9) systems provides a powerful tool for precisely modifying the human genome, thus revolutionizing the treatment of single-gene disorders.

In this talk, I will present recent work in my lab on developing new tools and methods for the design and optimization of CRISPR/Cas9 systems, and the efforts in developing a clinically applicable gene correction strategy for treating sickle cell disease (SCD), which is the first single-gene disorder with molecular understanding. We optimized CRISPR/Cas9 systems targeting the beta-globin gene, and systematically evaluated their on- and off-target cleavage in different cells. We also quantified the nuclease-induced gene modification rates in CD34+ cells from SCD patients, and demonstrated that CRISPR/Cas9 based genome editing is effective in generating normal hemoglobin (HbA) and reducing sickling hemoglobin (HbS). These studies significantly facilitated our pre-clinical investigation of SCD treatment using CRISPR/Cas9 and donor templates. The opportunities and challenges in developing nuclease-based genome editing strategies for treating single-gene disorders are discussed.