Docket #: S22-455

Muscle-specific Base Editor Enables Correction of Pathogenic Mutations in vivo for Dilated Cardiomyopathy

Stanford researchers have developed novel technology that combines AAVMYO, a muscle cell targeting viral vector, with CRISPR base editors to achieve targeted gene repair, showcasing over 70% correction of hereditary mutations in cardiomyocytes. The approach demonstrates significant promise in treating dilated cardiomyopathy, offering a potential cure for a condition with limited therapeutic options.

Dilated cardiomyopathy presents a significant challenge due to its prevalence and lack of effective treatments, making heart transplantation the only current option. Although there are heritable mutations, amenable to CRISPR-based gene therapy, challenges related to delivery of the editing complex and off-target concerns hamper the broad applicability of CRISPR agents in the heart. Stanford researchers have developed a solution by utilizing AAVMYO for precise delivery to heart muscle tissue and CRISPR base editors to correct heritable mutations in the Rbm20 gene. The technology achieves a remarkable repair rate, and has demonstrated efficacy in restoring normal cardiac function in mouse models.

Stage of Development

In vivo: researchers have repaired >70% of cardiomyocytes in two Rbm20 knock-in mouse models. Three months after injection, cardiac dilation and ejection fraction reach wild-type levels. Single-nuclei RNA sequencing uncovers restoration of the transcriptional profile across all major cardiac cell types and whole-genome sequencing reveals no evidence for aberrant off-target editing.

Applications

- Hereditary dilated cardiomyopathy

- Gene repair for various hereditary cardiac diseases

Advantages

- First therapy that could completely cure patients with monogenic, pathogenic DCM variants
- Precise targeting enhances specificity for heart muscle tissue
- Minimal off-target effects
- Twice as effective as AAV9 (gold standard)

Publications

- Grosch, M., Schraft, et al. (2023). Striated muscle-specific base editing enables correction of mutations causing dilated cardiomyopathy. *Nature Communications*, 14(1), 3714.

Patents

- Published Application: WO2024102811
- Published Application: 20260166179

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