Docket #: S21-459

CRISPR-based gene editing platform to treat FOXP3-mediated immune dysregulation

Stanford inventors have identified a therapeutic CRISPR-based gene editing strategy that restores expression of *Forkhead Box Protien 3* (*FOXP3*) isoforms that are disrupted in patients with Immunedysregulation, Polyendocrinopathy, Enteropathy X-linked Syndrome (IPEX). The *FOXP3* gene is required for regulatory T (Treg) cell function, immune tolerance, T cell homeostasis, and transiently affects effector T (Teff) cells. Disruption of *FOXP3* expression causes the severe and early onset development of multiple autoimmune phenotypes associated with IPEX. Current treatments for IPEX include pharmacological intervention and stem cell transplantation but are limited by low efficacy and unwanted side effects, or difficulties in donor matching and availability, and host rejection. To combat these limitations, researchers in the Pediatrics department developed a gene editing approach to insert functional *FOXP3* cDNA at the endogenous locus in patient-derived cells. This approach preserves the tightly choreographed regulatory mechanisms that govern appropriate *FOXP3* expression, such as precise spatio-temporal patterns and alternative splicing. This genetic construct is predicted to correct over 85% of IPEX-causing mutations in patients. Overall, this therapeutic approach has potential to accomplish genetic and phenotypic correction of the *FOXP3* mutations in IPEX patients through a novel CRISPR-based approach without the negative side effects associated with existing therapies.

Stage of Development
Research - *in vitro*

Applications

- Treatment for Immunedysregulation, Polyendocrinopathy, Enteropathy X-linked syndrome (IPEX)

Advantages

- Improved efficacy
- Fewer side effects than existing treatments
- More readily available than stem cell transplantation
- Preserves endogenous spatio-temporal expression of *FOXP3* in Tregs and Teffs
- Maintains alternative splicing events and isoform expression relevant to IPEX
- Autologous platform uses patient cells to limit risk of host rejection
- Restores expression of *FOXP3* in over 85% of IPEX patients
- Minimal off-target effects
- Construct contains a surface marker used clinically to select and track genetically engineered cells

Publications

- Goodwin, M., Lee, E., et al. (2020). CRISPR-based gene editing enables FOXP3 gene repair in IPEX patient cells. Science Advances, 6(19).

Patents

- Published Application: WO2023122099

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