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RESEARCH ARTICLE · BIOLOGY

CRISPR-Cas12a Base Editing Rescues Splicing Defects in a Cellular Model of Cystic Fibrosis

Ana Beatriz Souza[1], Daniel Kim[2]

[1] *University of São Paulo*
[2] *Stanford University*

ABSTRACT

Cystic fibrosis remains the most common lethal autosomal recessive disorder in populations of European descent, with the c.3849G>A splicing variant accounting for a substantial fraction of severe CFTR mutations. Using a cytosine base editor delivered via lipid nanoparticles, we achieved up to 64% on-target correction in primary patient-derived bronchial epithelial cells. Restored CFTR function was confirmed by transepithelial chloride current measurements and forskolin-induced swelling assays. Off-target editing, assessed by GUIDE-seq, remained within the threshold tolerated by current regulatory guidance. The work establishes a preclinical rationale for in vivo base-editing interventions in class II CFTR variants.

Keywords: *CRISPR, base editing, cystic fibrosis, CFTR, lipid nanoparticles*

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Authors

- **Ana Beatriz Souza** — University of São Paulo (ORCID 0000-0002-3333-0001)
- **Daniel Kim** — Stanford University

Abstract

Cystic fibrosis remains the most common lethal autosomal recessive disorder in populations of European descent, with the c.3849G>A splicing variant accounting for a substantial fraction of severe CFTR mutations. Using a cytosine base editor delivered via lipid nanoparticles, we achieved up to 64% on-target correction in primary patient-derived bronchial epithelial cells. Restored CFTR function was confirmed by transepithelial chloride current measurements and forskolin-induced swelling assays. Off-target editing, assessed by GUIDE-seq, remained within the threshold tolerated by current regulatory guidance. The work establishes a preclinical rationale for in vivo base-editing interventions in class II CFTR variants.

1. Introduction

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2. Methods

Methodological detail is preserved verbatim from the accepted manuscript. The production service has rendered this HTML, PDF, and JATS galley using Pandoc 3.1.11.1 and WeasyPrint with the journal's house CSS template.

3. Results

The findings, figures, and tables of the original submission are reproduced here. Readers should consult the PDF galley for the authoritative typeset version.

4. Discussion

3849G>A splicing variant accounting for a substantial fraction of severe CFTR mutations

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