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A new drug combination rescues a rare Cystic Fibrosis mutation in patient tissue

University of Toronto researchers in the laboratory of Dr. Christine Bear, together with collaborators at SickKids Hospital (Toronto, Canada) and Proteostasis Therapeutics (Cambridge, Massachusetts), used computer simulations, cell-based systems and patient tissue to interrogate the consequences of a rare Cystic Fibrosis (CF) disease-causing mutation in the *CFTR* gene: c.3700 A>G (also called ΔI1234_R1239) and subsequently develop a novel mechanism-based therapeutic strategy.

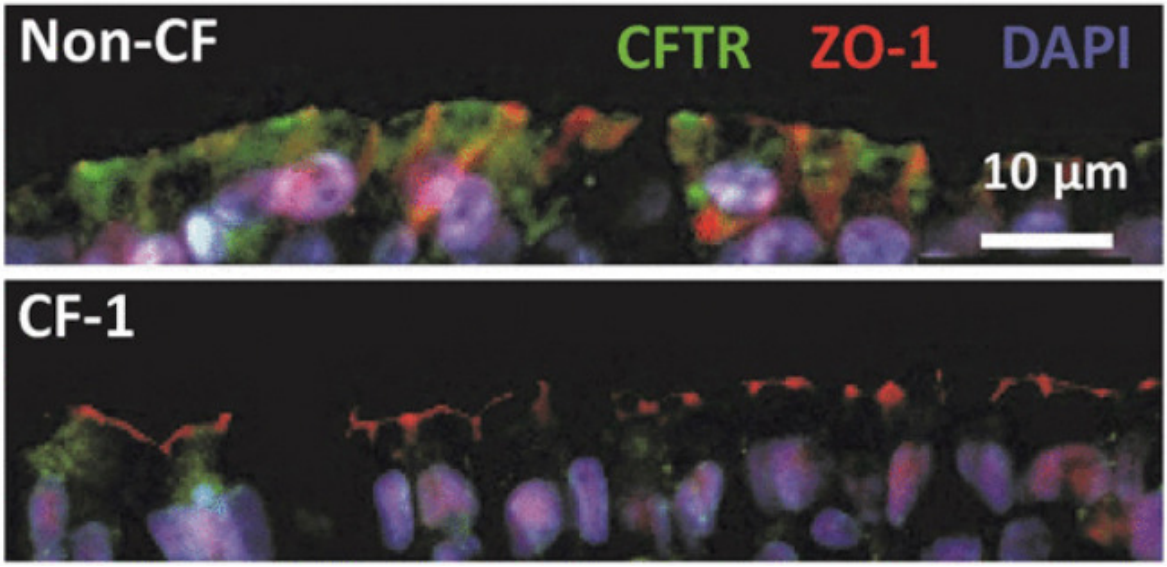

Fig. 1. Comparison of CFTR expression and localization in healthy versus CF-affected tissues.
Top panel: Immunofluorescence showing expression and localization of normal CFTR (green) on primary nasal tissue obtained from a healthy, non-CF family member. Tight junction protein ZO-1 (red) and cell nuclei (DAPI) are also labeled for comparison as landmarks; scale bar represents 10 µm. Bottom panel: Lower expression and inappropriate localization of the rare variant (ΔI1234_R1239-CFTR, green) from a family member with CF (i.e. Patient CF-1).

In brief, this study determined that the rare variant exhibited several protein defects that were comparable to the most common CF mutation, ΔF508; suggesting that drugs designed for ΔF508 (i.e. ORKAMBI®) may also be effective for ΔI1234_R1239. However, patient-derived tissue from individuals bearing this rare mutation showed that additional unique defects were present (i.e. low CFTR protein abundance) and that ORKAMBI® alone would not be sufficient. In collaboration with Proteostasis Therapeutics, the authors determined that an investigational small molecule, an "amplifier" (PTI-CH), aimed at enhancing CFTR protein abundance, improved the rescue effect of ORKAMBI®, first in a CRISPR/Cas9 edited bronchial epithelial cell line and then in nasal epithelial tissue from individuals homozygous for this rare mutation.

This study highlights the importance of drug testing using relevant, patient-specific tissues for informing therapeutic strategies for CF individuals with rare mutations.

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Publication

Orkambi® and amplifier co-therapy improves function from a rare CFTR mutation in gene-edited cells and patient tissue.
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