Impact of routine pulmonary medications on rescued CFTR in cystic fibrosis cells

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Background

- Cystic fibrosis (CF) is a complex genetic disorder requiring management of multiple organ systems.
- Individuals with CF often adhere to complex medication regimens targeting pulmonary function, infection control, and nutritional support.
- The cornerstone of therapy lies in rescuing the function of the defective cystic fibrosis transmembrane conductance regulator (CFTR) protein.
- The potential for interactions between these modulators and other prescribed CF medications could significantly impact treatment efficacy and inform clinicians in optimizing medication regimens for individuals with CF.

Methods

- CFBE cells expressing the ΔF508 CFTR mutation were cultured on permeable inserts to establish an air-liquid interface (ALI).
- Cells were treated with elexacaftor/tezacaftor or vehicle. Azithromycin, tobramycin, pulmozyme, and hypertonic saline were added to the treatment, either alone or in combination.
- CFTR function was measured using the Ussing chamber, a device that can measure trans-epithelial chloride ion secretion, which is directly dependent on CFTR activity.

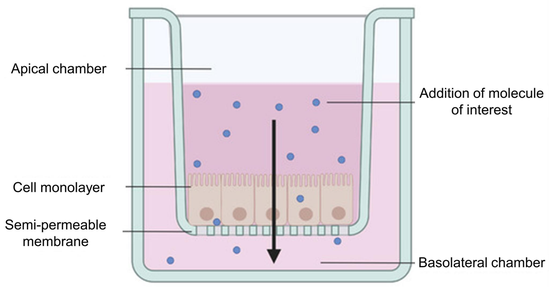

Diagram of ALI. Reference: S. Masloh et al., Challenges and Opportunities in the Oral Delivery of Recombinant Biologics. Pharmaceutics 15, (2023).

Objective

The goal of this project was to test if common pulmonary medications affect modulator-rescued CFTR function in CF airway epithelia.

Pathophysiology of Cystic Fibrosis (CF)

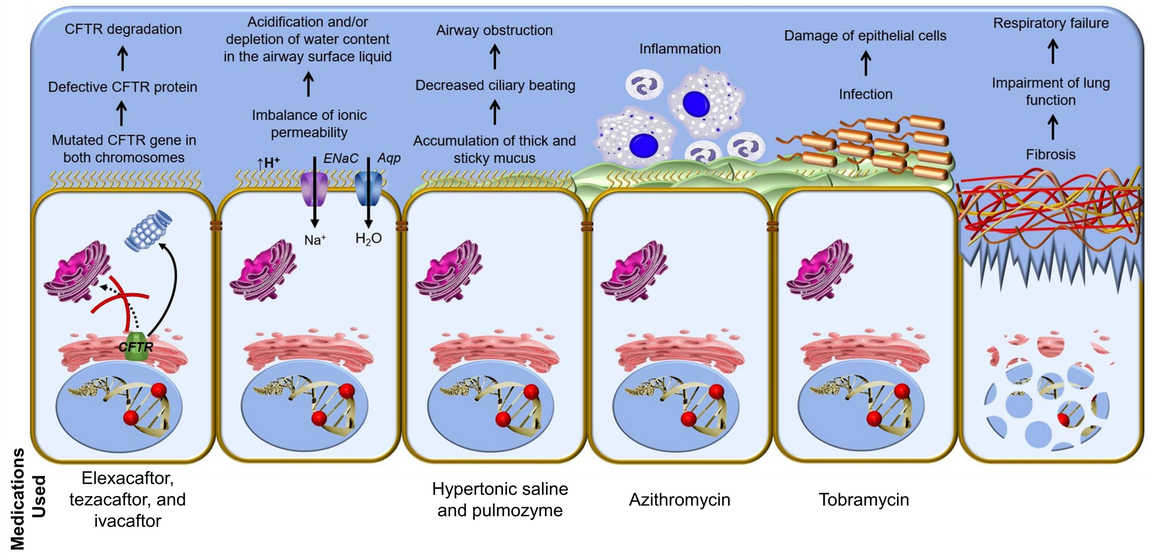

Figure 1. Pathophysiology of Cystic Fibrosis. Cellular mechanism of cystic fibrosis begins with the defective CFTR gene and shortage of CFTR channel at the plasma membrane. A vicious cycle of airways obstruction, inflammation and infection leads to epithelial damage, lung remodeling and end-stage lung disease. ENaC, epithelial Na+ channel; Aqp, aquaporin. Reference: M. Lopes-Pacheco, CFTR Modulators: Shedding Light on Precision Medicine for Cystic Fibrosis. Front Pharmacol 7, 275 (2016).

Ussing Chamber

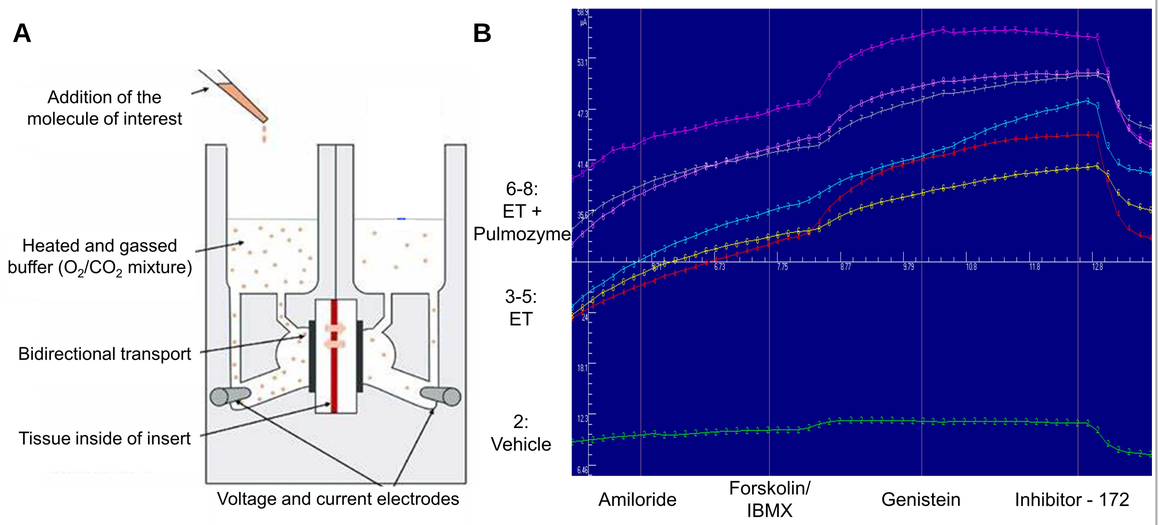

Figure 2. Example of an Ussing chamber run. **A.** Diagram showing example of an Ussing chamber. Reference: Reprocell: Ussing Chamber. **B.** CFBE cells were treated with Vehicle (Line 2, green), ET only (Lines 3-5, blue, red, and pink), or ET and Pulmozyme (Lines 6-8, yellow, grey, and magenta) prior to run. Chemicals added during run included amiloride (inhibitor of sodium transport), forskolin/IBMX (activator of CFTR), genisten (CFTR potentiator), and inhibitor-172 (CFTR-specific inhibitor). X-axis is time (minutes), Y-axis is current (μA).

Ussing Data

Treatment	CFTR-Dependent Isc (μA/cm²)	p-value vs ET only
Vehicle	1.16 ± 0.73	2.24E-11
Elexacaftor/tezacaftor only (ET, 5 μM each)	3.8 ± 1.56	N/A
ET + Azithromycin (5 μM)	2.86 ± 2.00	0.057
ET + Tobramycin (200 μM)	3.07 ± 0.99	0.068
ET + Azithromycin (5 μM)/ Tobramycin (200 μM)	3.00 ± 0.60	0.063
ET + 3% Saline	3.88 ± 1.71	0.47
ET + Pulmozyme (0.5 mg/mL)	3.71 ± 2.88	0.46

Table 1. CFTR function following various treatments. F508del CFBEs were treated with vehicle or elexacaftor/tezacaftor (ET) followed by co-treatment with common pulmonary medications. CFTR function was then calculated using CFTR-dependent short-circuit current (isc). Data displayed as mean ± standard deviation and compared using one-tailed Student's t-test.

Results

- ΔF508 CFBEs treated with CFTR modulators showed significantly increased CFTR function compared to vehicle-treated cells ([1.16 μA ± 0.73] vs. [3.80 μA ± 1.56] $p < 0.05$.
- Co-treatment with azithromycin, tobramycin, pulmozyme, or hypertonic saline did not significantly alter modulator-rescued CFTR function (Table 1).
- Combination therapy with azithromycin and tobramycin also had no significant effect (Table 1).

Conclusions

- Common pulmonary medications did not significantly alter rescued CFTR function in vitro.
- These findings suggest that these medications are unlikely to interfere with CFTR modulator therapy.
- Further studies utilizing clinical trial data and/or primary patient cell models would be useful to confirm these observations.
- Continuation of this work would help providers decide on continuing vs reducing co-treatments in patients taking CFTR modulators.