

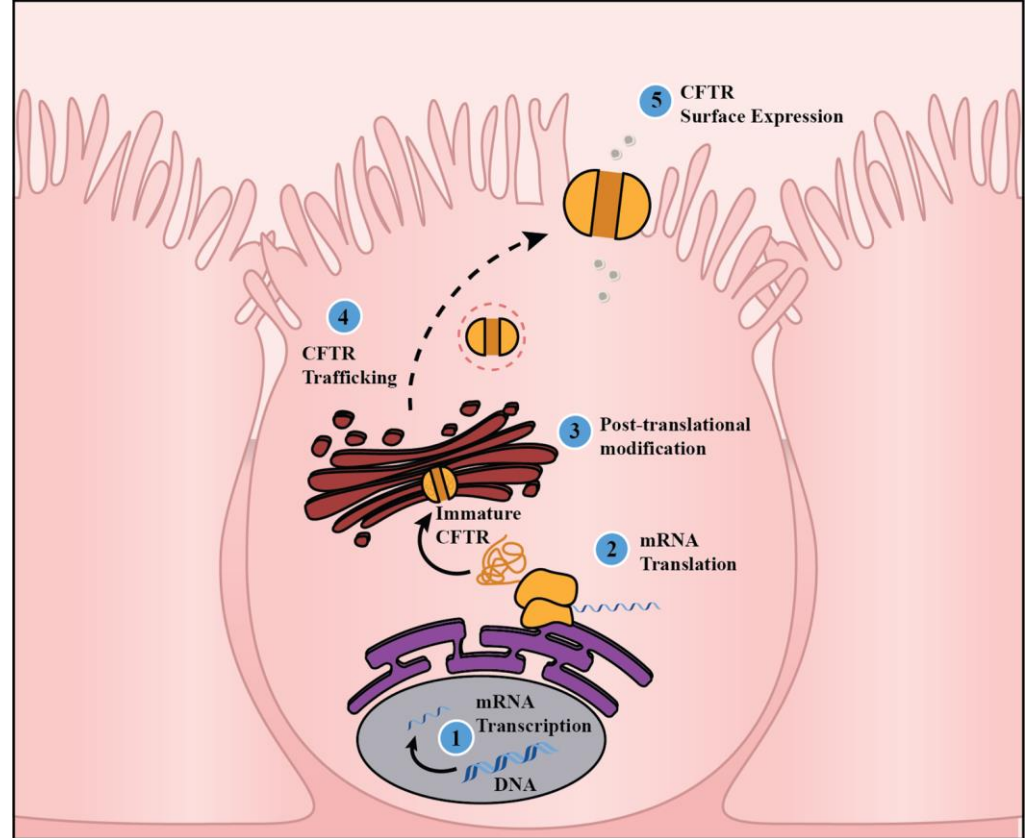
Engineered mutant α -ENaC subunit mRNA delivered by lipid nanoparticles reduces amiloride currents in cystic fibrosis - based cell and mice models

Anindit Mukherjee, Kelvin D. MacDonald, Jeonghwan Kim,
Michael I. Henderson, Yulia Eygeris, and Gaurav Sahay



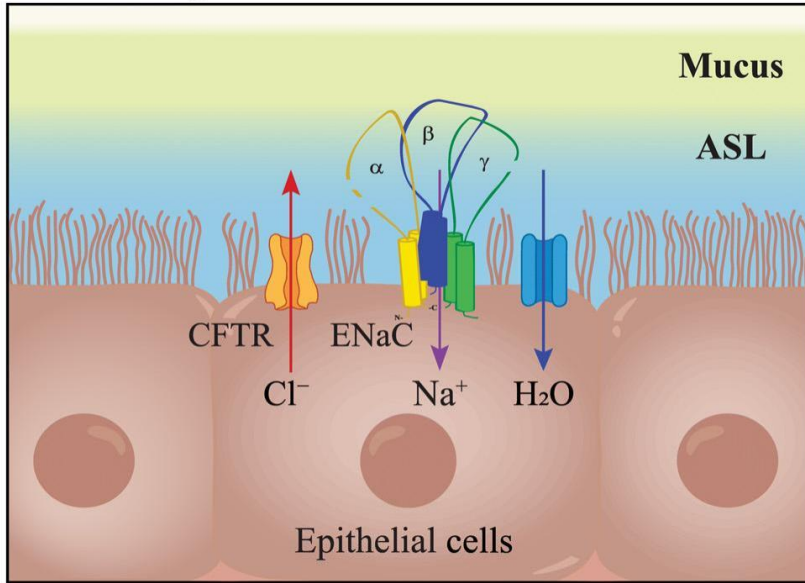
Introduction

- What is Cystic Fibrosis (CF)?
- Who does CF affect?
- Which ion channel is mutated?

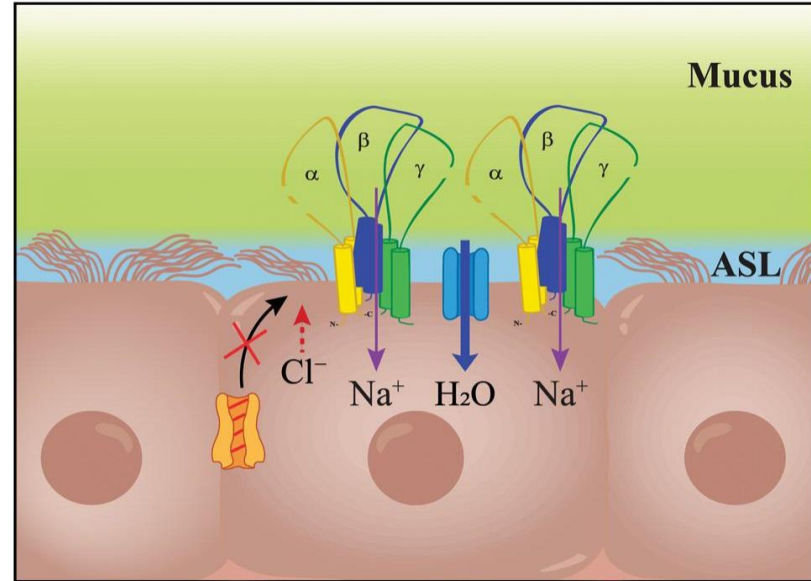


Normal vs. Cystic Fibrotic Lung

A Normal lung



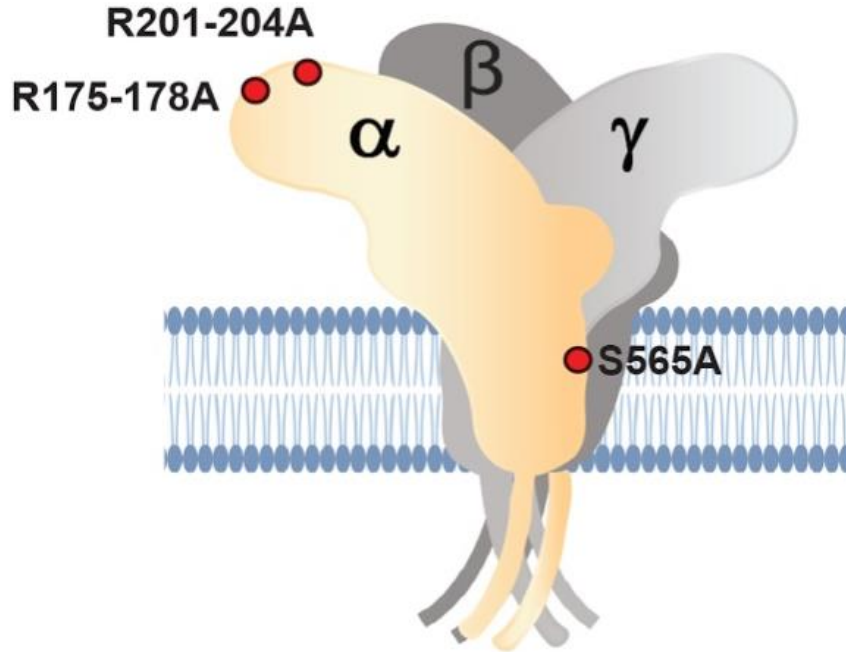
B Cystic fibrosis lung



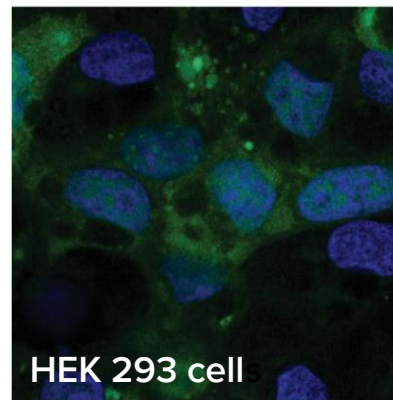
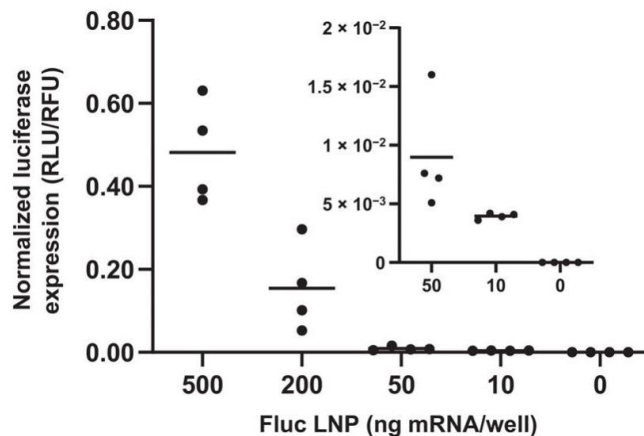
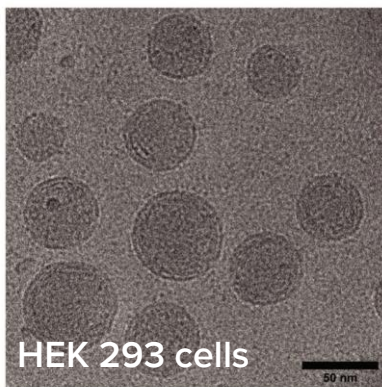
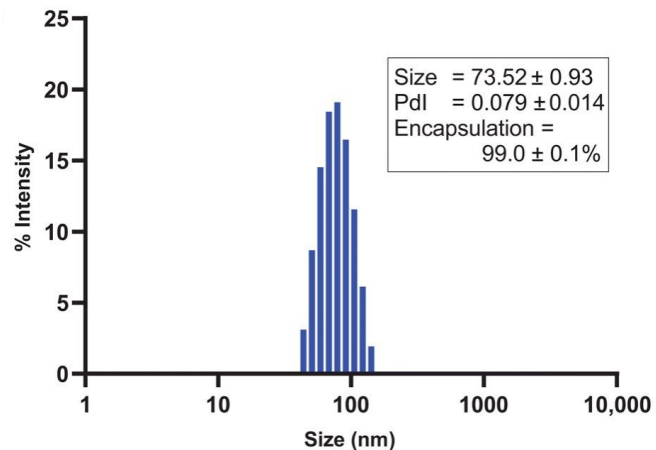
Our Hypothesis:

We hypothesized that ENaC activity can be reduced by deploying mRNA that encodes for a channel-inactivating ENaC α (α_{mut} ENaC) subunit packaged inside lipid-based nanoparticles (LNPs) for delivery.

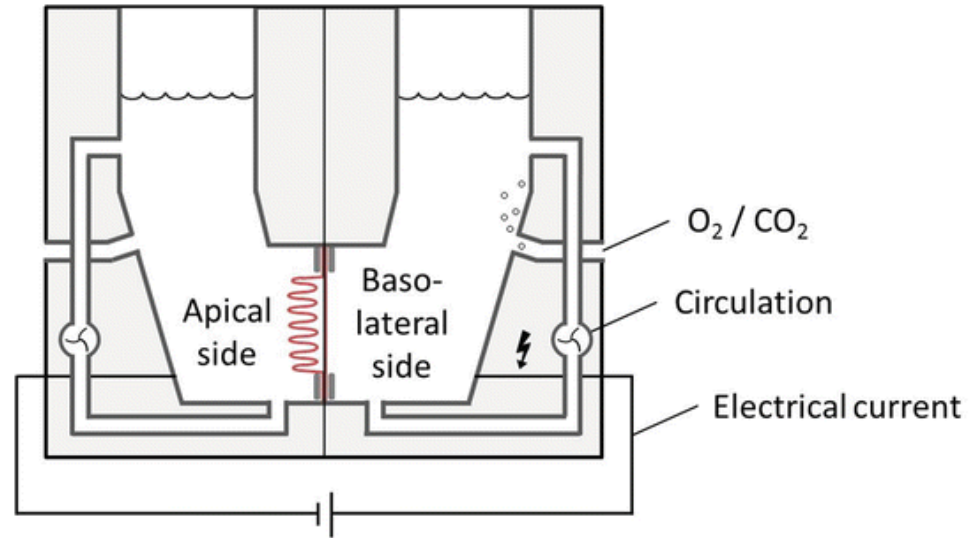
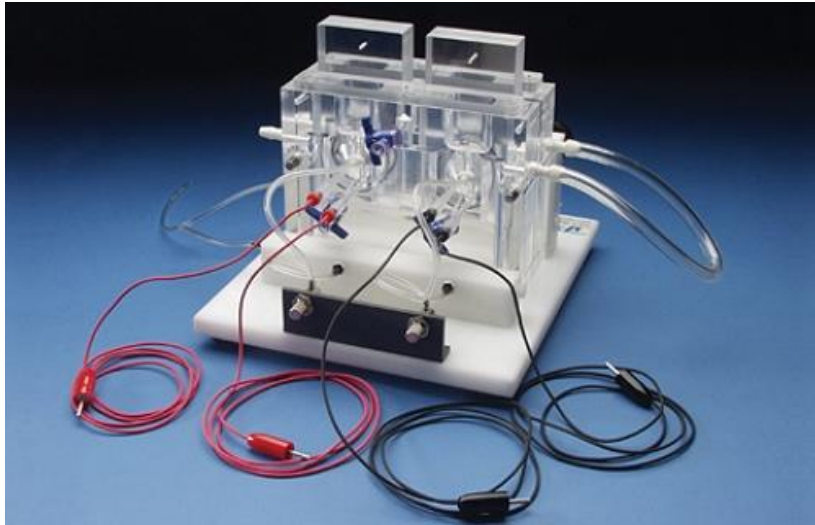
α -ENaC subunit mRNA channel inactivation



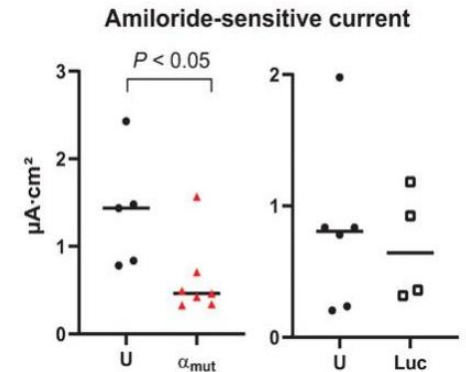
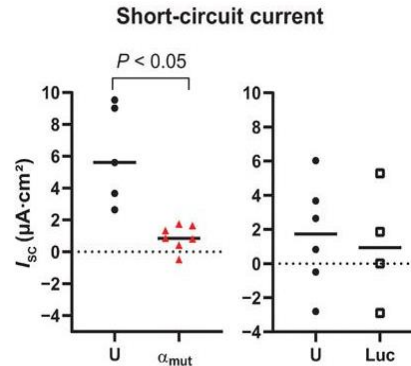
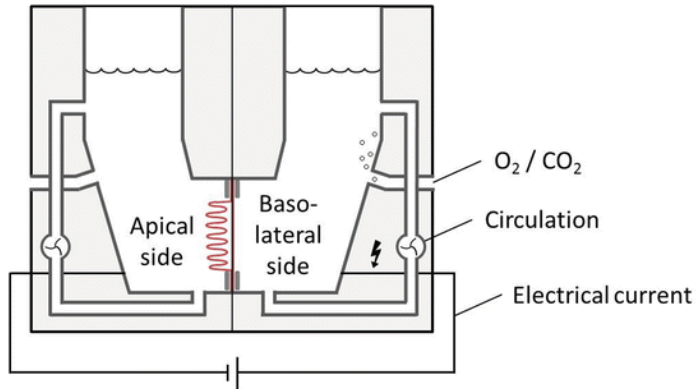
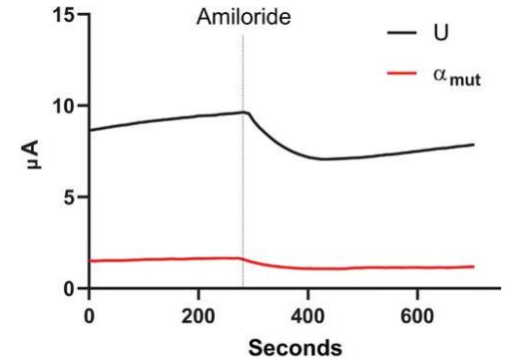
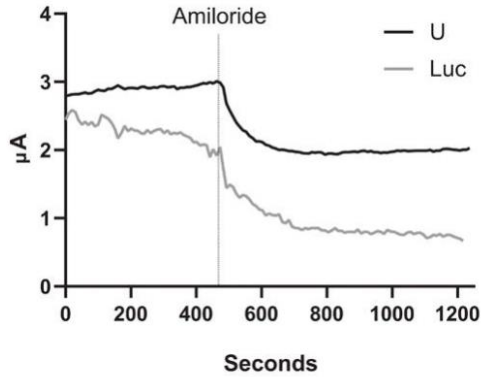
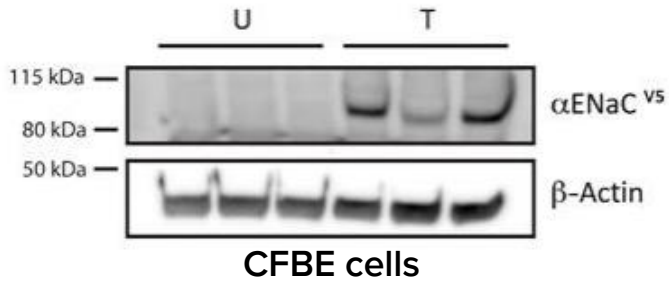
LNP characterization and *in vitro* mRNA transfection.



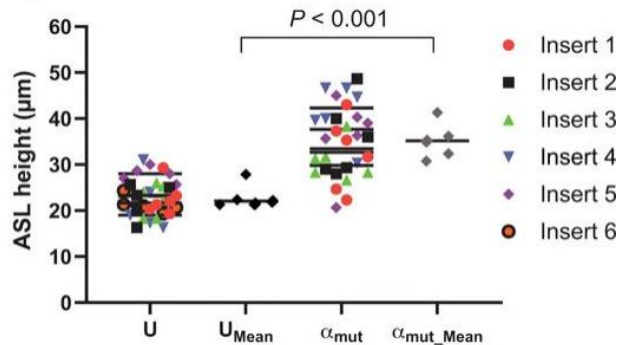
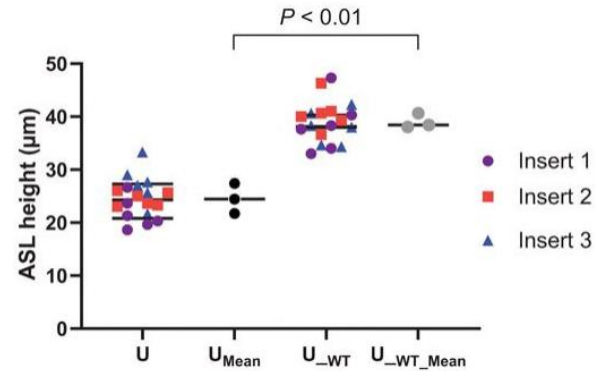
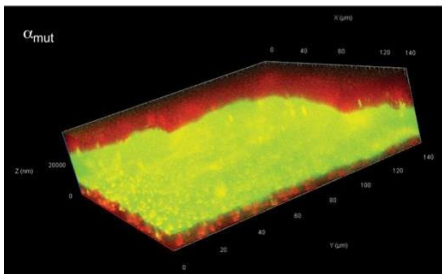
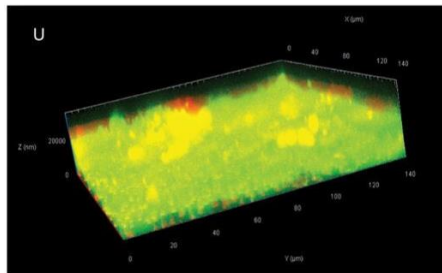
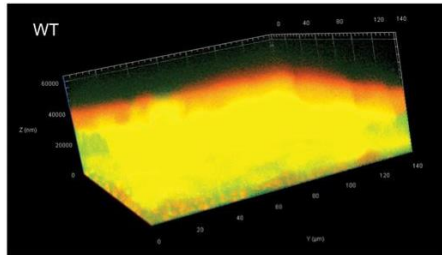
Ussing Chamber



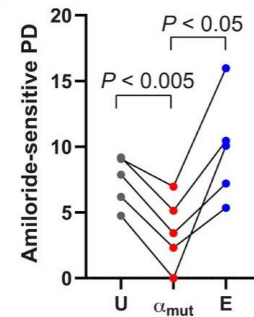
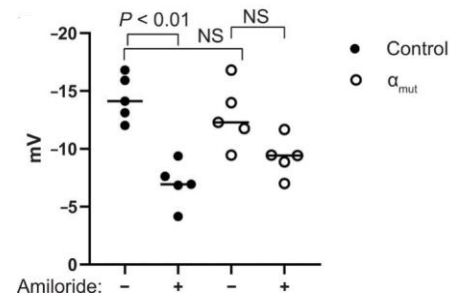
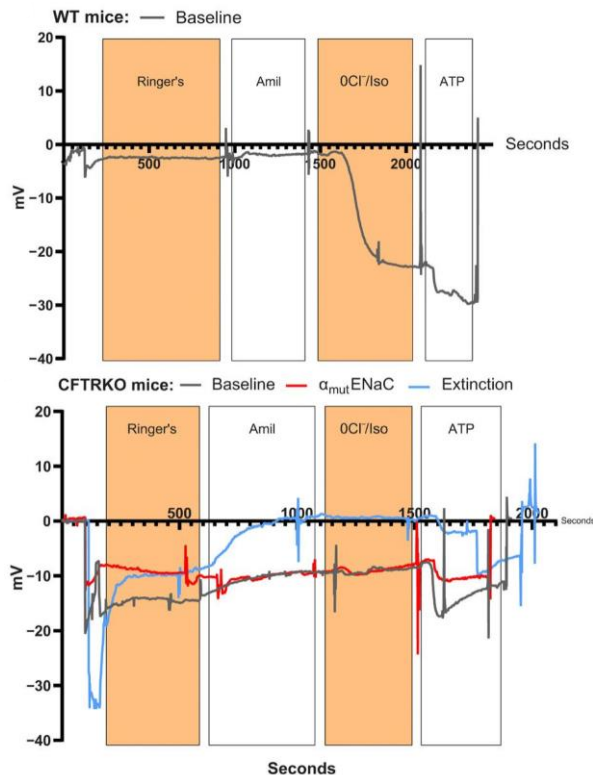
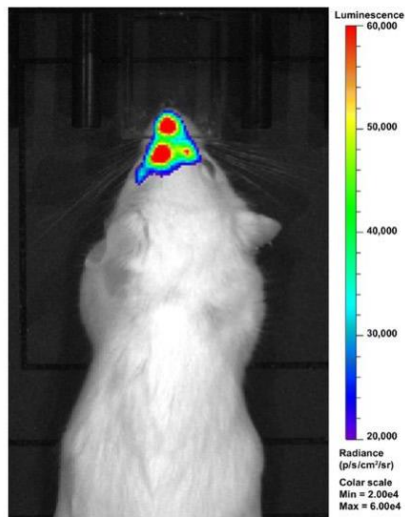
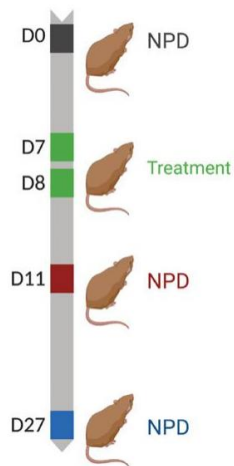
α_{mut} ENaC transfection reduces amiloride-sensitive ENaC current in airway cell.



α_{mut} ENaC transfection increases ASL height in airway cells.



α_{mut} ENaC transfection reduced amiloride-sensitive NPD in CFTRKO mice.

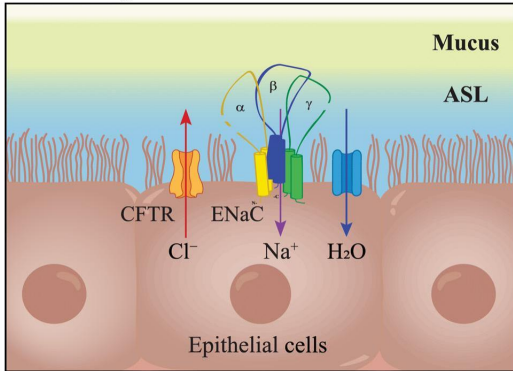


Summary

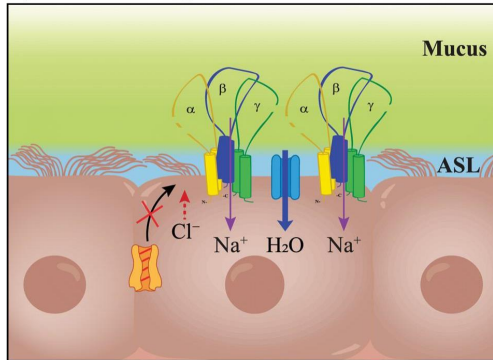
- Dysregulation of ENaC activity is common across many CFTR gene mutations.
- α_{mut} ENaC subunit mRNA can successfully be encapsulated within LNPs.
- α_{mut} ENaC transfection:
 - Reduces amiloride sensitive ENaC current *in vitro* and *in vivo*.
 - Increase ASL height in airway cells.

Conclusions

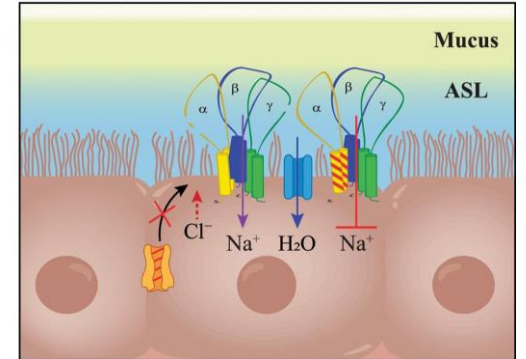
A Normal lung



B Cystic fibrosis lung



C Our intervention



Our results showcase the promise of mRNA therapeutics as a potential universal treatment of CF regardless of underlying CFTR mutation.

Acknowledgements

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