1. Department of Chemical Engineering, The Sargent Centre for Process Systems Engineering, University College London, Torrington Place, WC1E 7JE
2. Department of Neuroscience, Physiology and Pharmacology, Medical Sciences Building, University College London, Gower Street, WC1E 6BT

A multicellular modelling framework for airway epithelial fluid and ion transport: implications for cystic fibrosis gene therapy

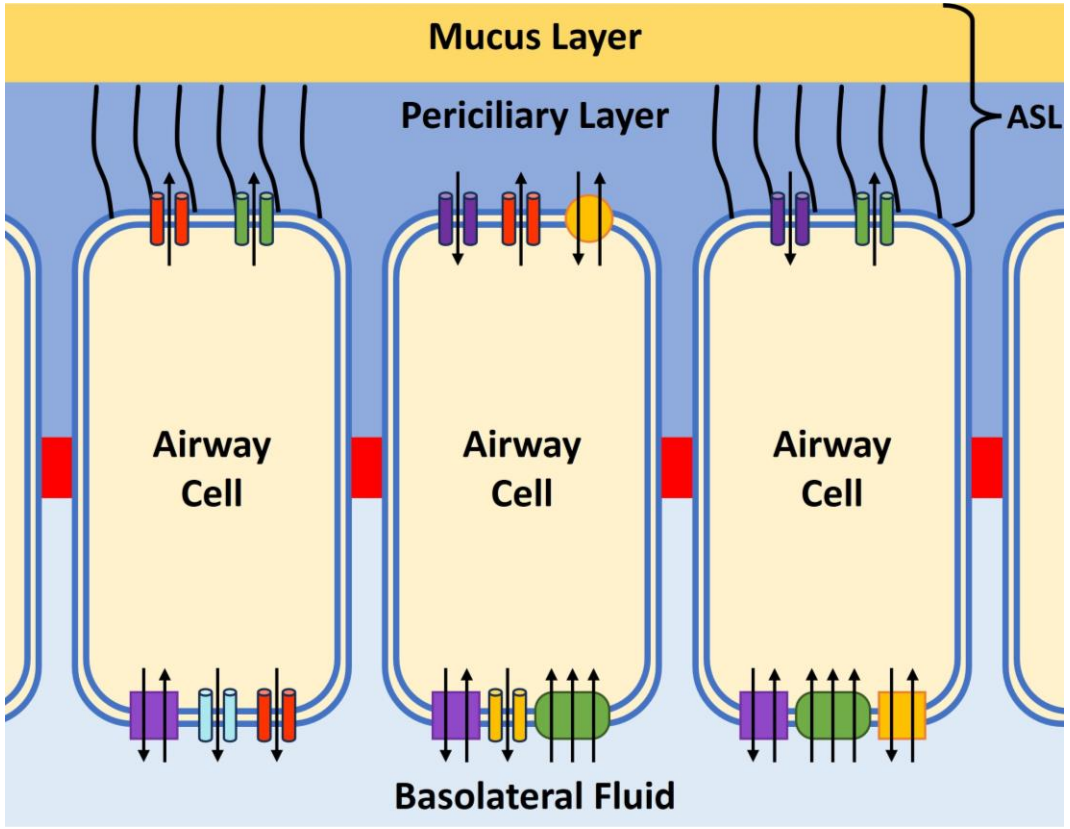
Omar Hamed[1,2], Guy W.J. Moss[2], & Vivek Dua[1]

Sargent Centre for Process Systems Engineering

UCL ENGINEERING
Change the world

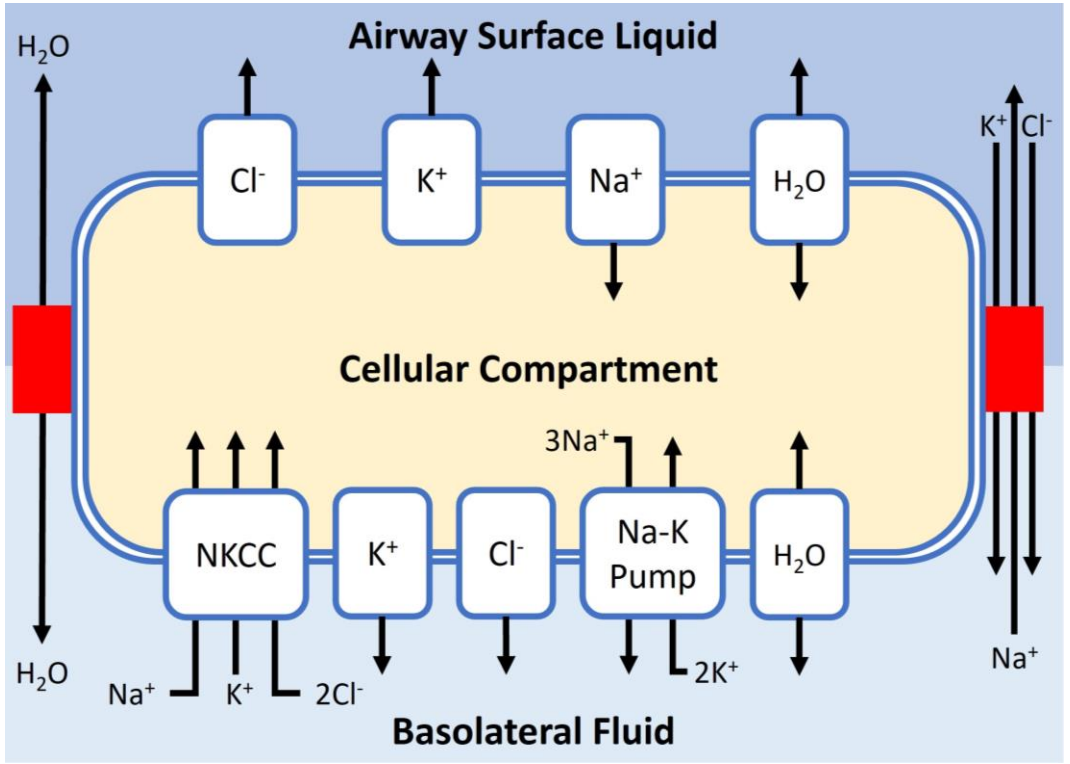
Modelling fluid/ion transport in airway epithelia

- Mucociliary clearance facilitated by thin-film airway surface liquid (ASL)
- Fluid and ion transport controlled by:
  - Ion channels
  - Transporters
  - Tight junctions
- Computational modelling can aid analysis of complex processes



Modelling fluid/ion transport in airway epithelia

- Mucociliary clearance facilitated by thin-film airway surface liquid (ASL)
- Fluid and ion transport controlled by:
  - Ion channels
  - Transporters
  - Tight junctions
- Computational modelling can aid analysis of complex processes



BUT… almost all models treat airway epithelium as single, idealised cell!

Modelling fluid/ion transport in airway epithelia

Goldman-Hodgkin-Katz Flux:

$$I_{ion} = P_{ion} {z_{ion}}^2 \frac{V_m F^2}{RT} \frac{a_i - a_o e^{(-z_{ion} F V_m / RT)}}{1 - e^{(-z_{ion} F V_m / RT)}}$$

Rate of Change of State Variables:

$$\frac{dx_j}{dt} = \sum \left(J_j^{influx} - J_j^{efflux} \right)$$

Na^+/K^+-ATPase Steady-State Turnover Rate:

$$v_{NaK} = \frac{\alpha_1^+ \alpha_2^+ \alpha_3^+ \alpha_4^+ - \alpha_1^- \alpha_2^- \alpha_3^- \alpha_4^-}{\Sigma}$$

Compartment Osmolarities:

$$OSM_j = [Na^+]_j + [Cl^-]_j + [K^+]_j + [\psi]_j$$

$Na^+/K^+/2Cl^-$ Cotransporter Steady-State Turnover Rate:

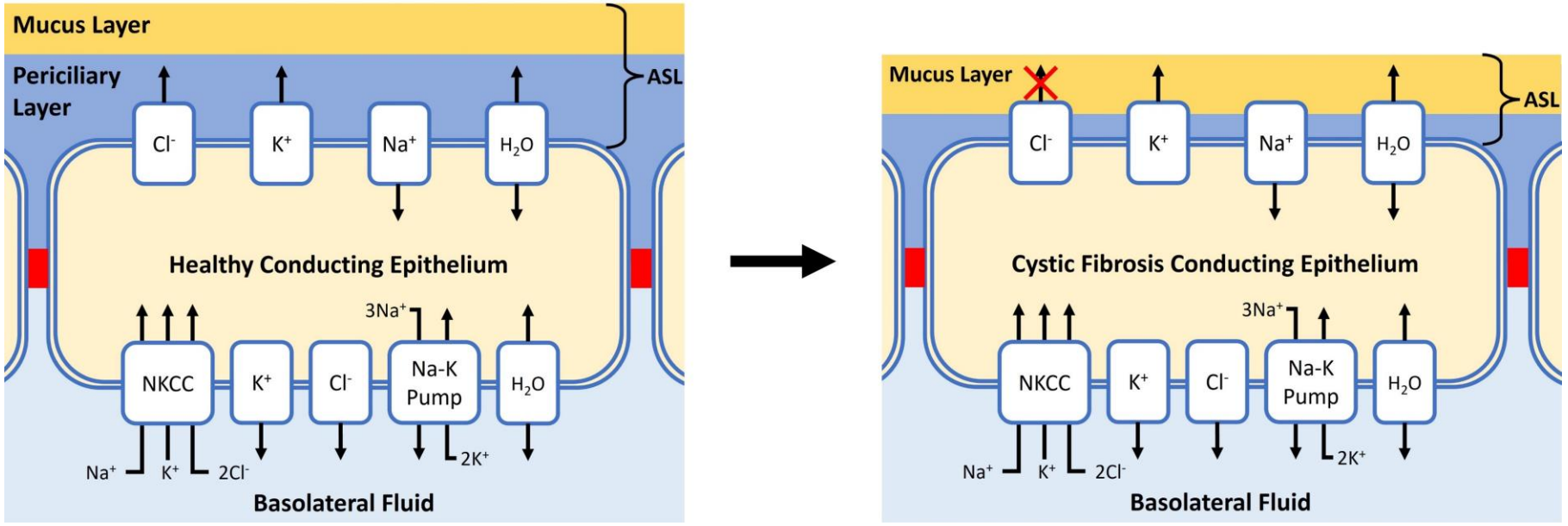
$$v_{NKCC} = \frac{k_f^{full} k_f^{empty} [Na^+]_s [K^+]_s [Cl^-]_s^2 - k_b^{full} k_b^{empty} [Na^+]_i [K^+]_i [Cl^-]_i^2}{\sum_{n=1}^{16} Z_{NKCC}^n}$$

Water Flux:

$$J_{H_2O} = P_{H_2O} v_{H_2O} \left(OSM_j - OSM_{j+1} \right)$$

Cystic fibrosis: at a glance

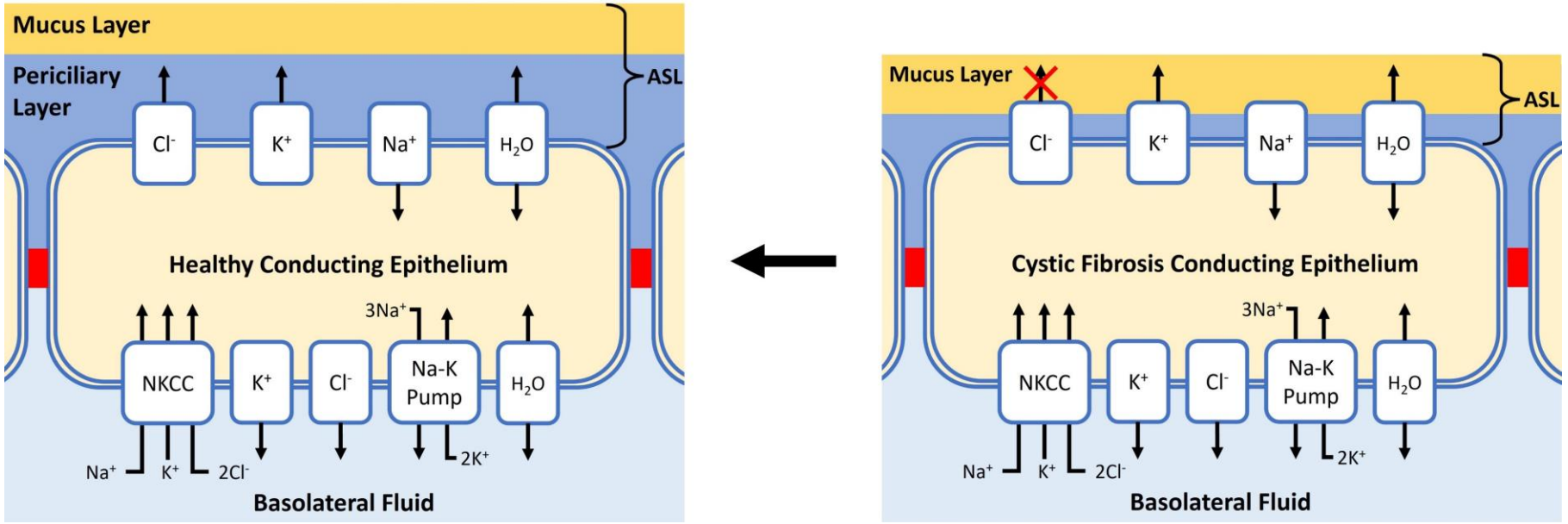
- Disease pathogenesis (dehydration theory):
  - Loss-of function mutations in CFTR anion channel
  - Reduced anion conductance → ASL dehydration → Chronic infection



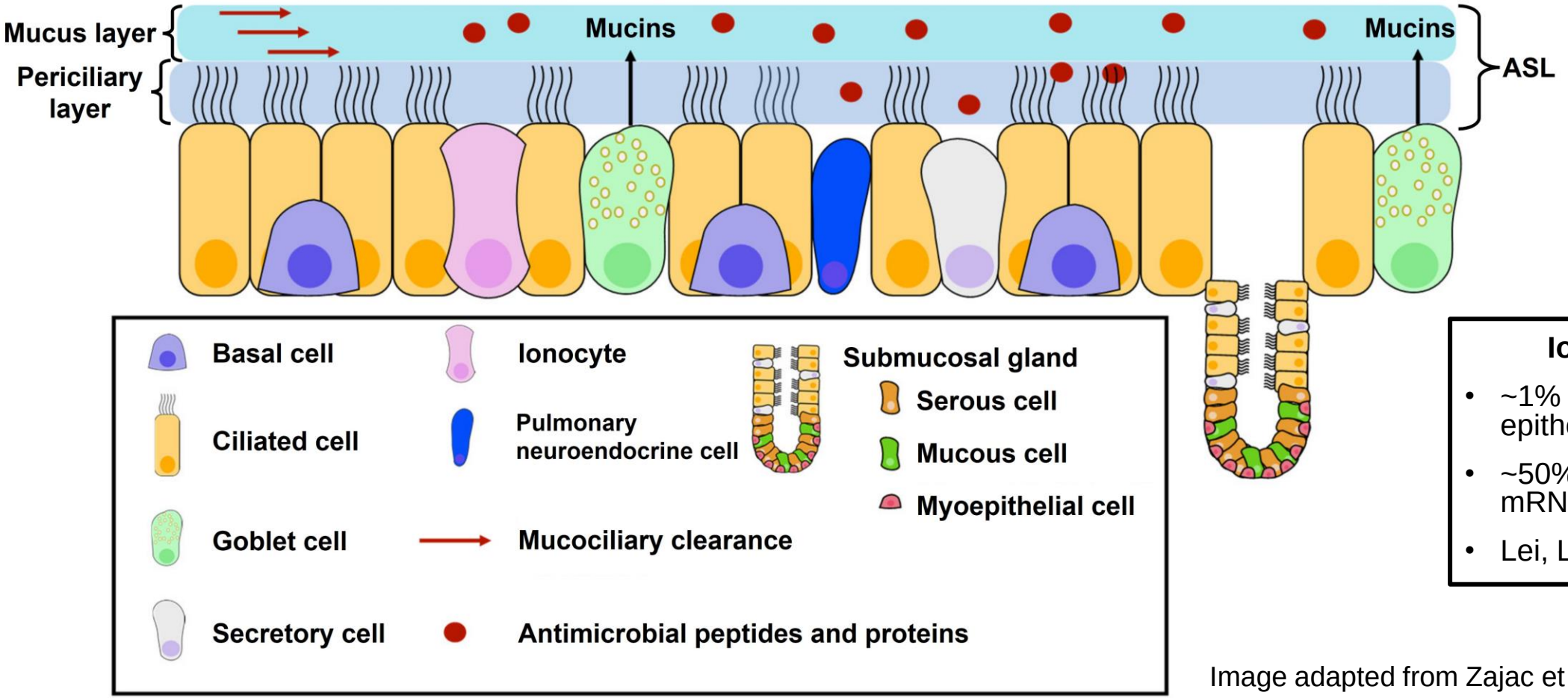
**Reduced HCO_3^- conductance also likely to impact pH regulation*

Cystic fibrosis: gene therapy

- Gene therapy (delivery):
  - Provide correct copies of the *CFTR* gene to cells
  - BUT… 1) limited efficiency and 2) we cannot reach every cell



The multicellular airway epithelium

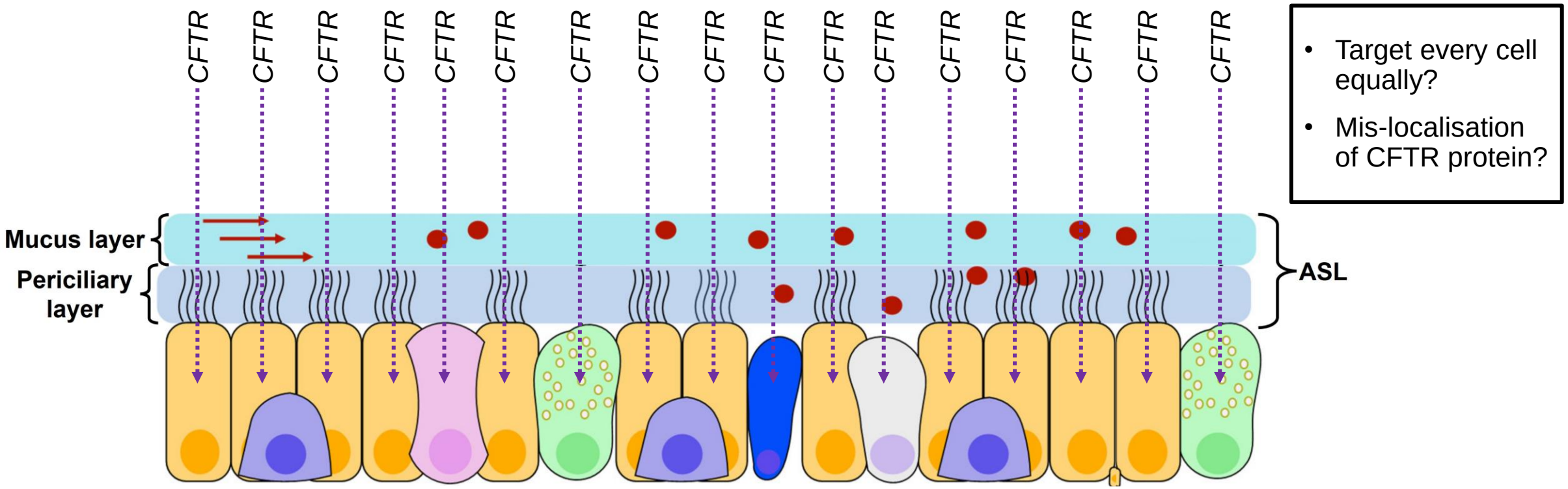


Ionocytes

- ~1% of airway epithelial cells
- ~50% of CFTR mRNA transcripts
- Lei, L., et al., (2023)

Image adapted from Zajac et al. (2021)

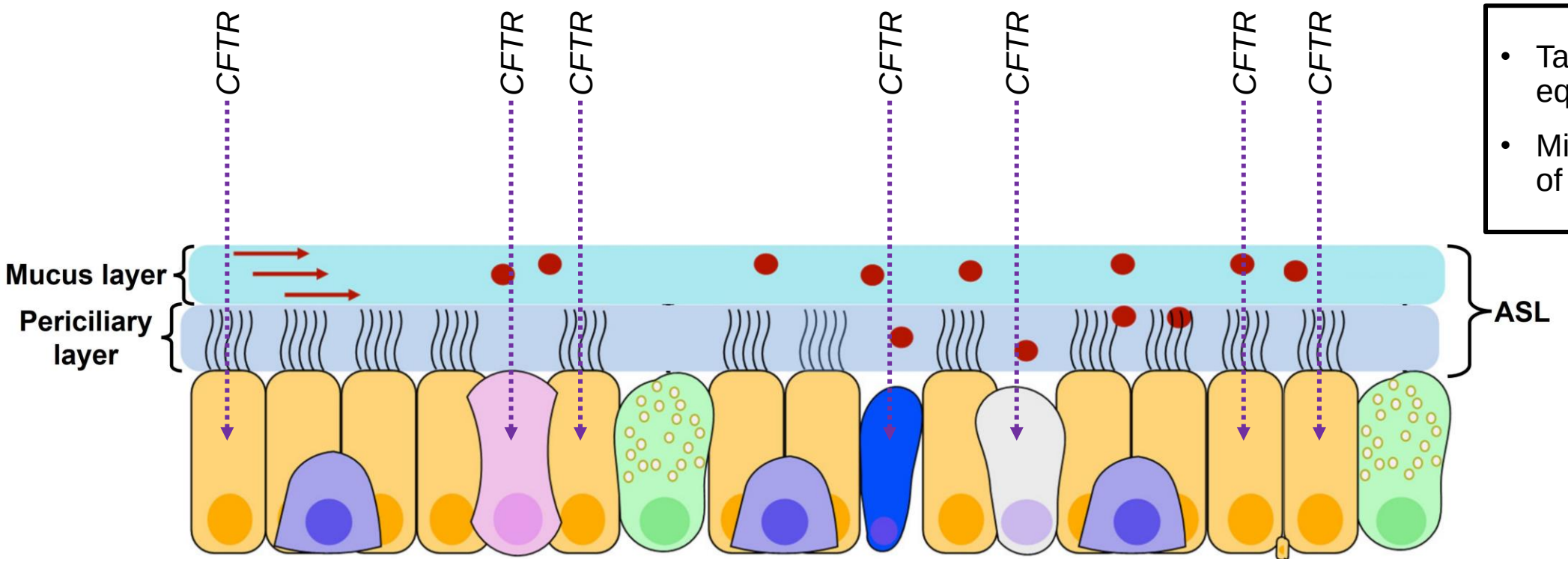
Gene therapy in the multicellular airway



- Target every cell equally?
- Mis-localisation of CFTR protein?

Image adapted from Zajac et al. (2021)

Gene therapy in the multicellular airway

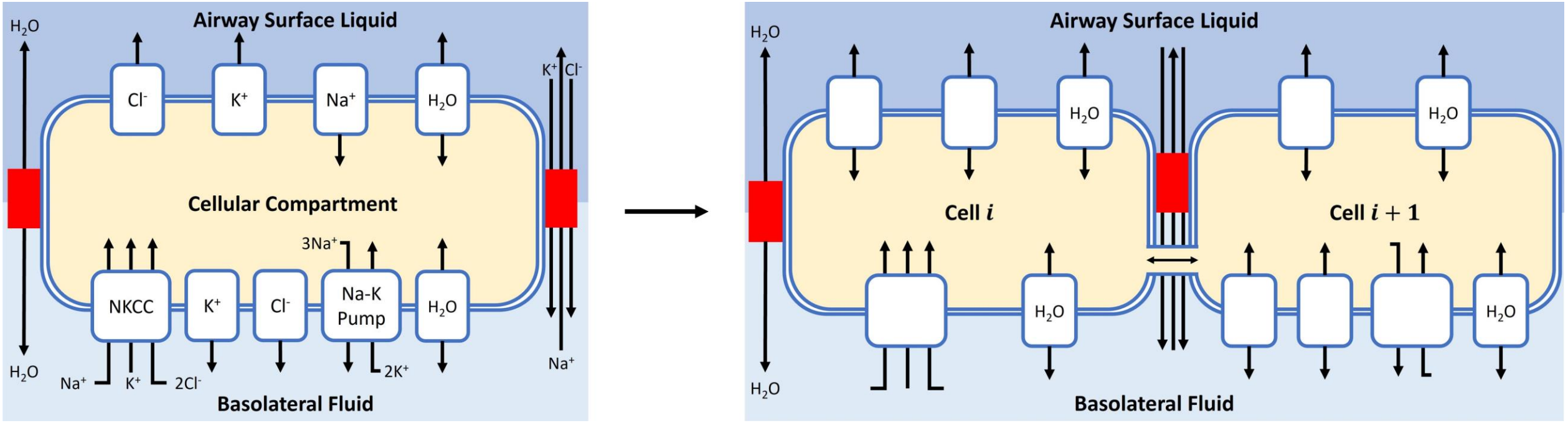


- Target every cell equally?
- Mis-localisation of CFTR protein?

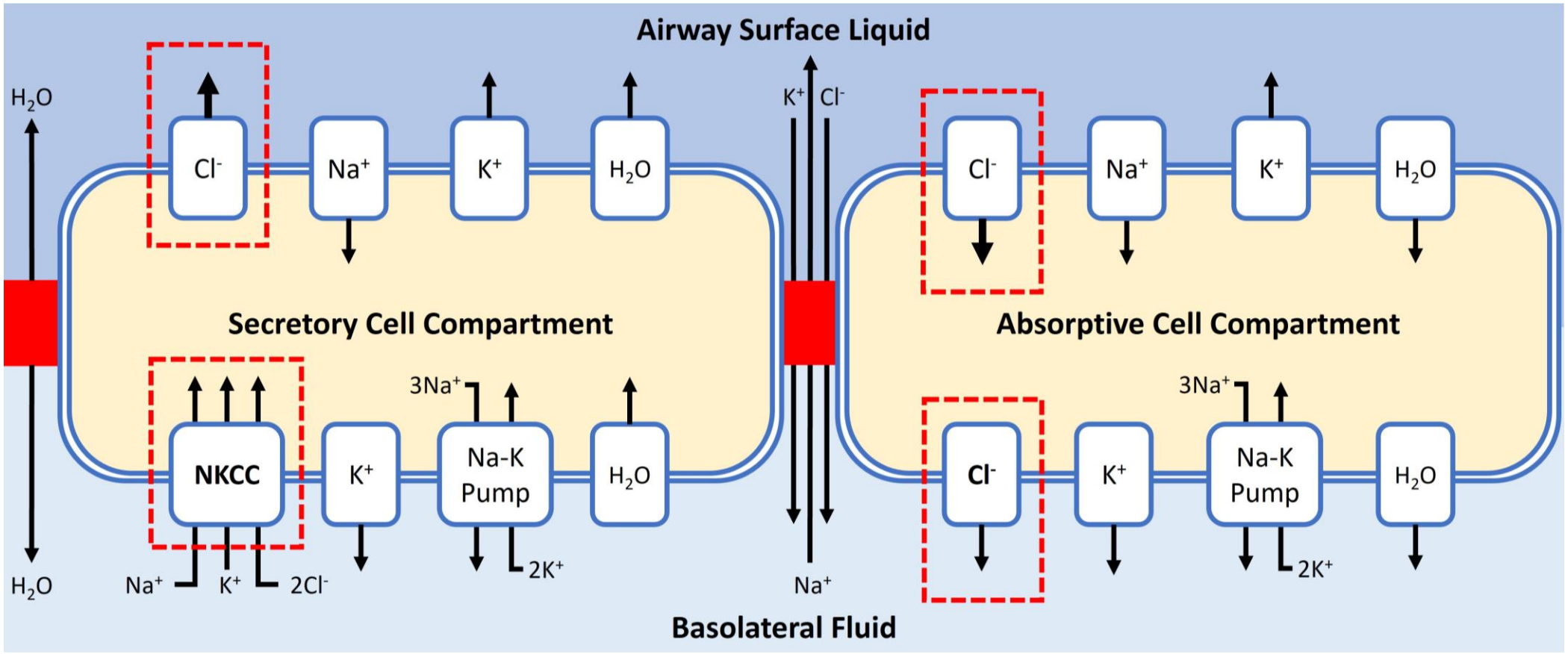
Image adapted from Zajac et al. (2021)

A framework for multicellular modelling of airway epithelia

- Based on the equivalent electrical circuit and fluid/ion fluxes



A cell-type dependent role for CFTR in secretion/absorption of Cl^-

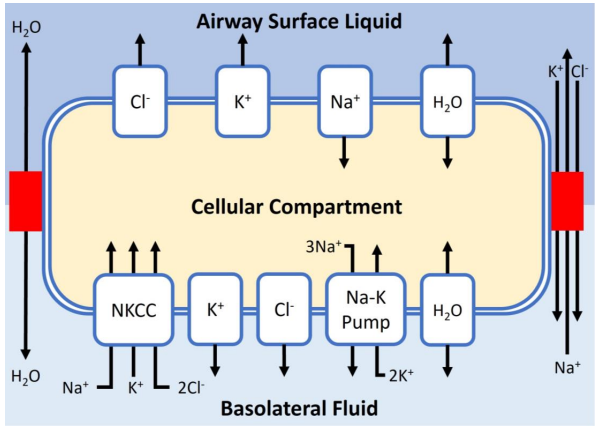


CF gene therapy in a two-cell model

	Scenario	Cells affected	Localisation	ASL Depth (μm)
1	Gene therapy returns apical Cl^- and Na^+ permeability to normal level…	**in every cell**	**-**	[illegible]
2		in every cell	but increases basolateral Cl^- in every cell (1:1 apical to basolateral)	[illegible]
3		in every cell	but increases basolateral Cl^- in every cell (2:1 apical to basolateral)	[illegible]
4		in every cell	but increases basolateral Cl^- in every cell (4:1 apical to basolateral)	[illegible]
5		**in secretory cell ONLY**	**-**	[illegible]
6		in absorptive cell ONLY	-	[illegible]
7		in secretory cell ONLY	but increases basolateral Cl^- in secretory cell (1:1 apical to basolateral)	[illegible]
8		in absorptive cell ONLY	but increases basolateral Cl^- in absorptive cell (1:1 apical to basolateral)	[illegible]

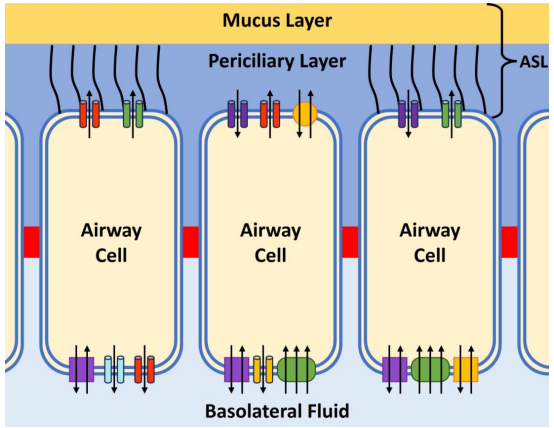
Table 1: Secretory-absorptive model outputs after simulating the target effects of gene therapy across eight different scenarios. Scenarios highlighted in bold (1 and 5) are predicted to most likely to result in adequate ASL rehydration.

Summary



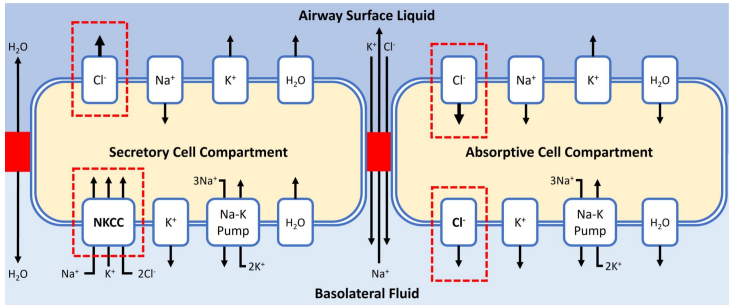
Single-cell models have had previous success in enhancing CF understanding

- Not an accurate representation of epithelium and limited application



Multicellular modelling provides a way to…

- Understand cell-type specific contributions to overall ASL regulation
- Investigate how to influence ASL hydration in CF by targeting specific cells



A secretory-absorptive model of airway epithelial fluid/ion transport…

- Highlights cell-type specific role for CFTR for secretion/absorption of Cl^-
- Can be used to investigate gene delivery outcomes

Thank you for listening!

Please visit me at Poster #20 to find out more.

Acknowledgments:

- Professor Vivek Dua
- Dr. Guy W.J. Moss
- Dr. David C.H. Benton
- Dr. Paola Vergani
- Dr. Arthur Mitchell
- Maria-Cristina Ardelean
- Saidi Li
- Jyosthna Lunavath

References:

- Zajac, M., et al., Airway Surface Liquid pH Regulation in Airway Epithelium Current Understandings and Gaps in Knowledge. Int J Mol Sci, 2021. 22(7).
- Lei, L., et al., CFTR-rich ionocytes mediate chloride absorption across airway epithelia. The Journal of Clinical Investigation, 2023. 133(20).