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In sickness and in health: Modelling the human airways

Dr Lindsay Marshall

Healthy or sick - human airways are complicated

- The airways function to conduct air for respiration… but are so much more than a conducting system

- Challenges for modelling…

- Three distinct anatomical regions
- Huge surface area
- Exposed continuously to outside
- Maintain a controlled biome, not sterility

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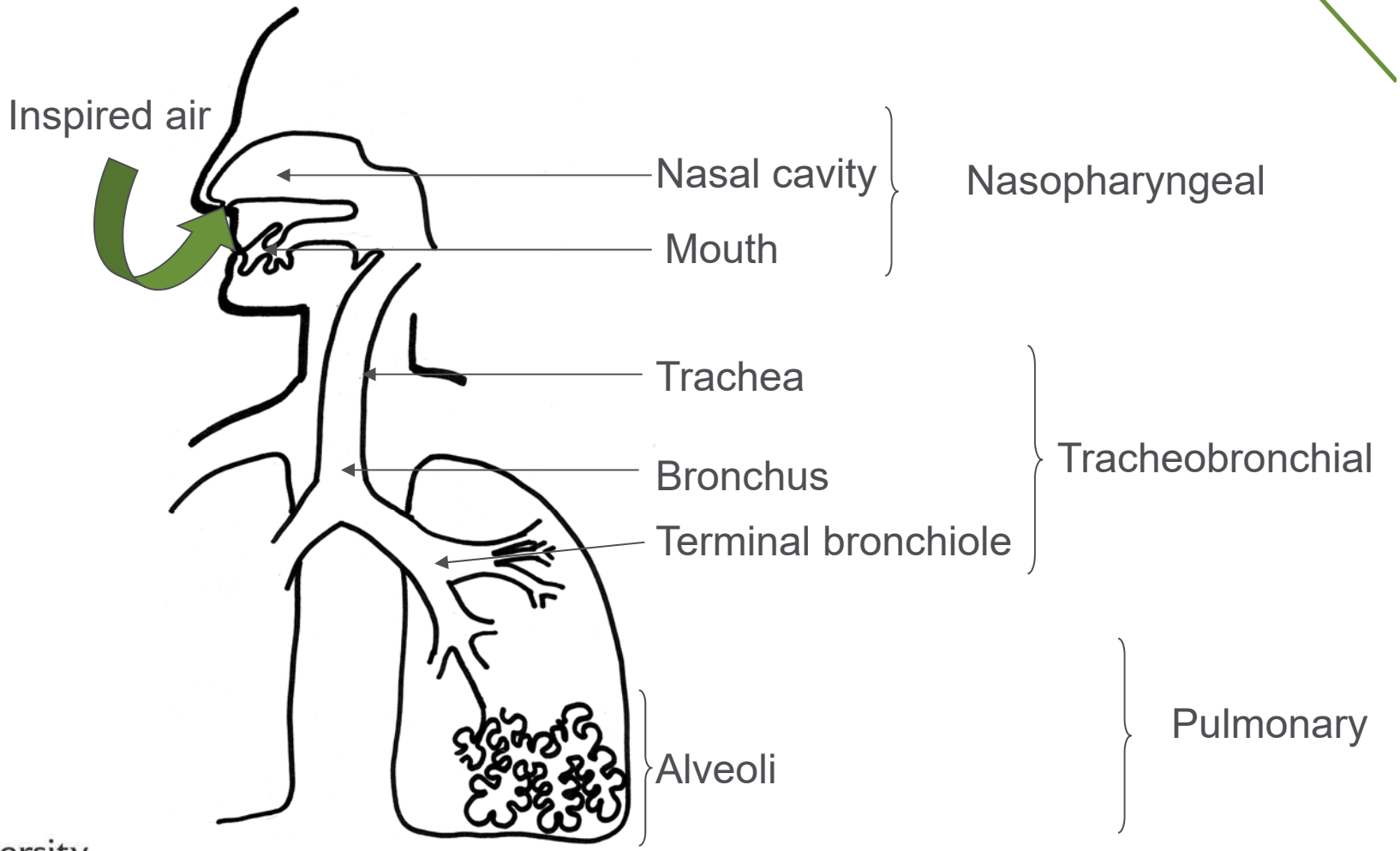
Anatomy of the human airways



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A Multicellular Mosaic

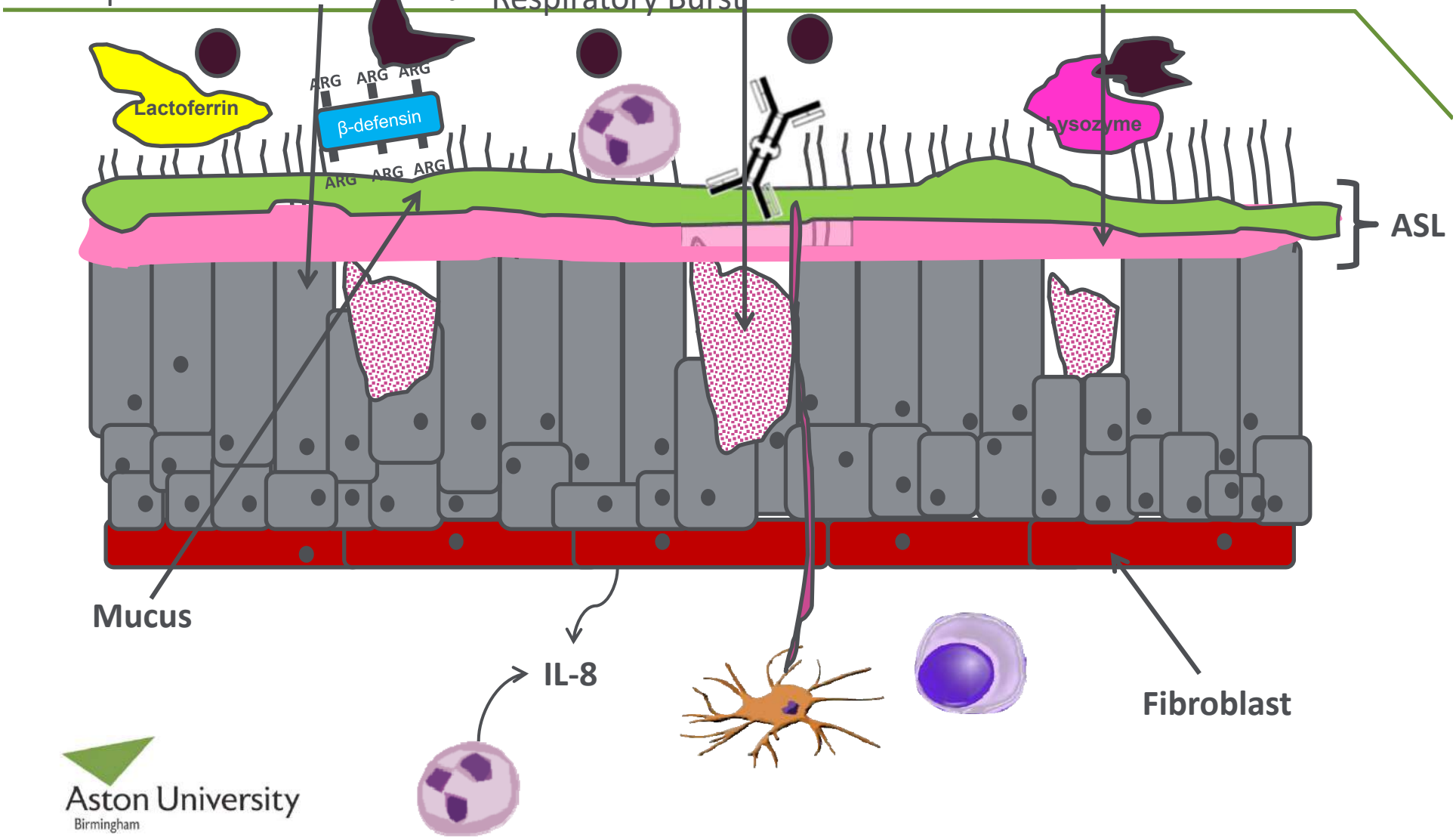
Inhale

- Small cationic peptide
- Form pores
- Sequester iron

- Phagocytosis
- Respiratory Burst

- Dimeric Ab
- Block pathogen binding

- Degrades glycosidic linkage of bacterial cell wall peptidoglycans



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Cellular composition in healthy human airways

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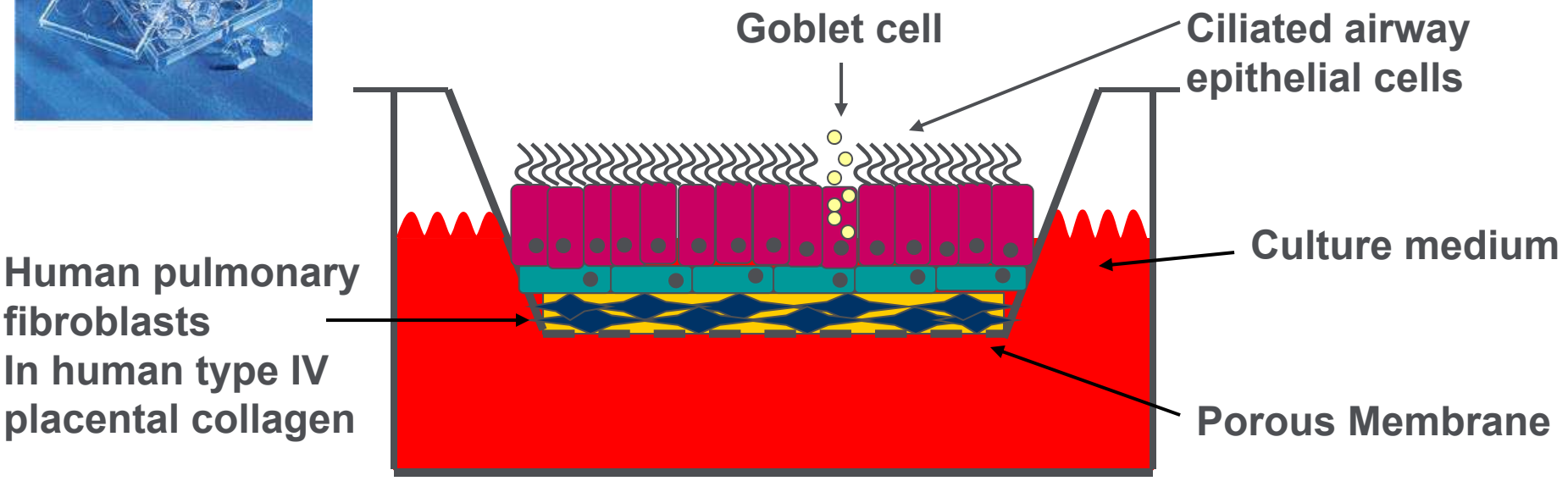
Aston's co-culture model of healthy human airways



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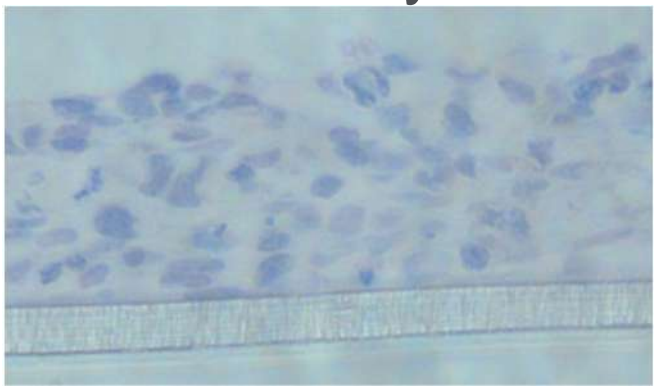
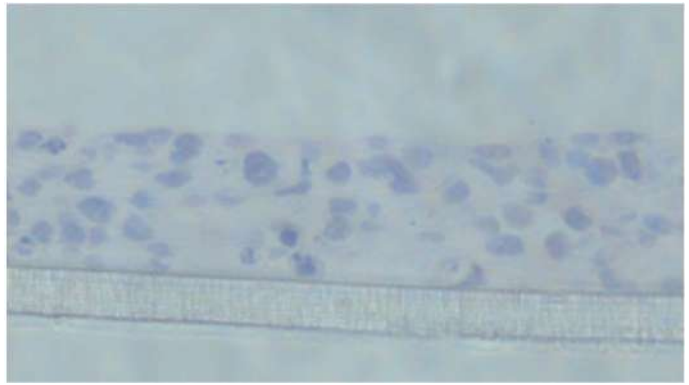
ALI produces a stratified, differentiated epithelium

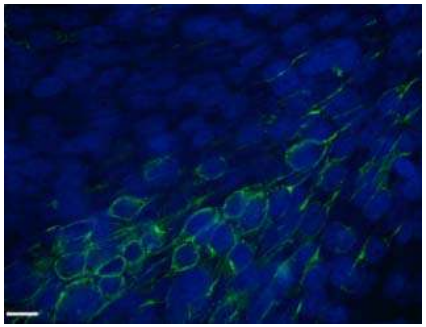
Healthy



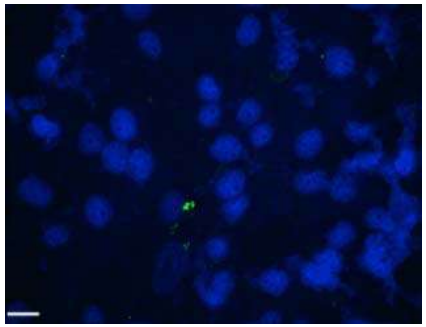
Sick



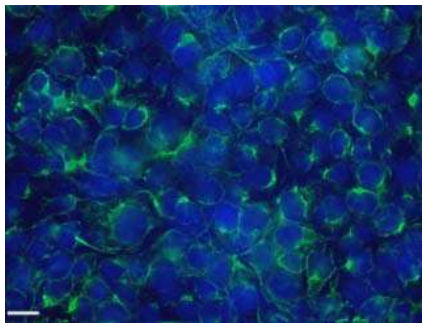
Differentiated



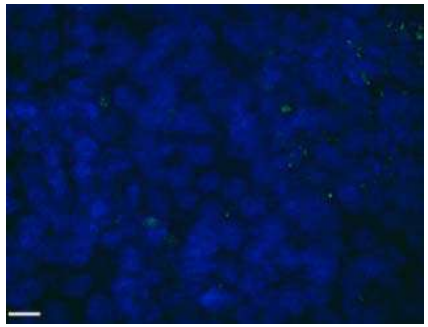
Basal



Differentiated



Basal



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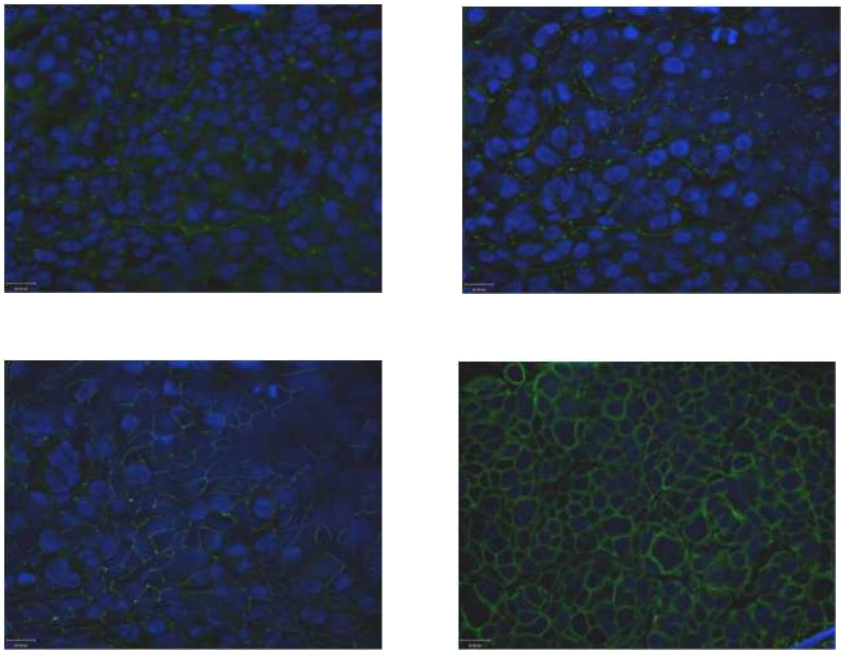
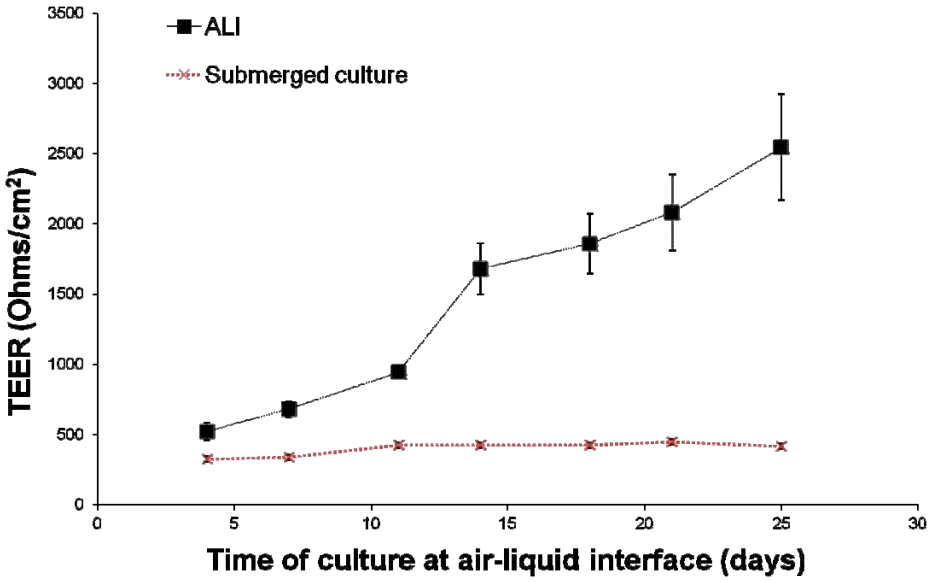
ALI produces a tight, resistant barrier

Tight junction proteins apically



TEER



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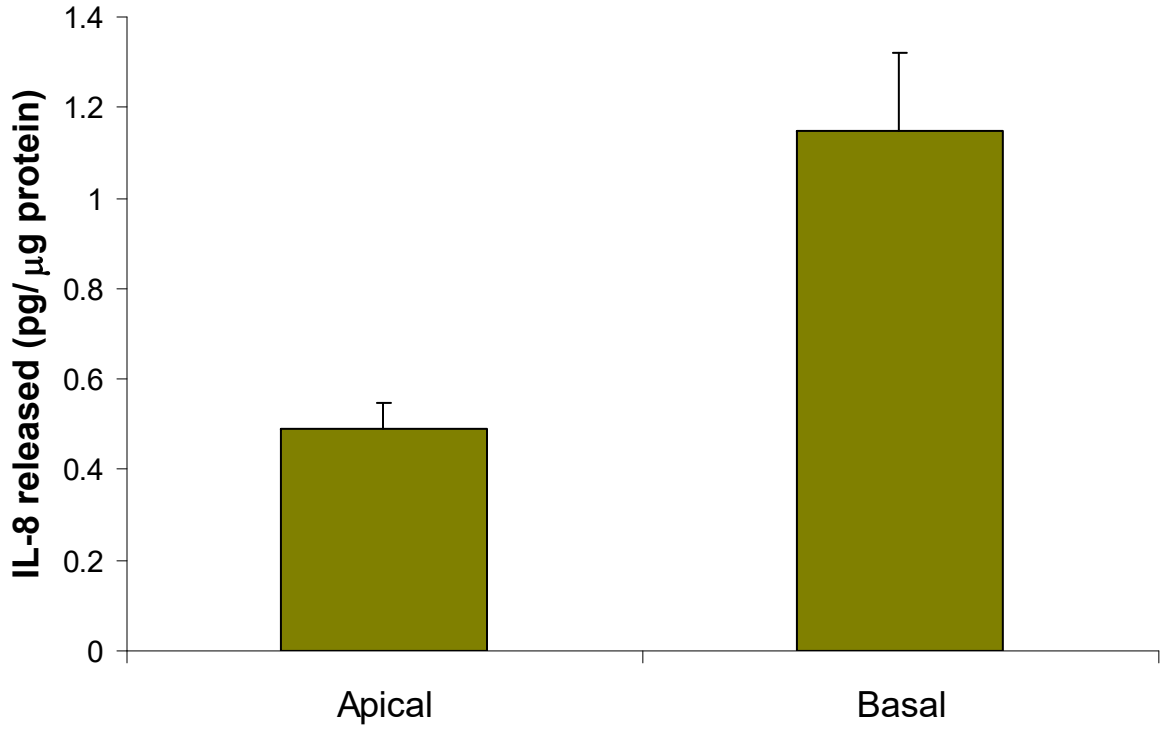
ALI permits analysis of where responses happen



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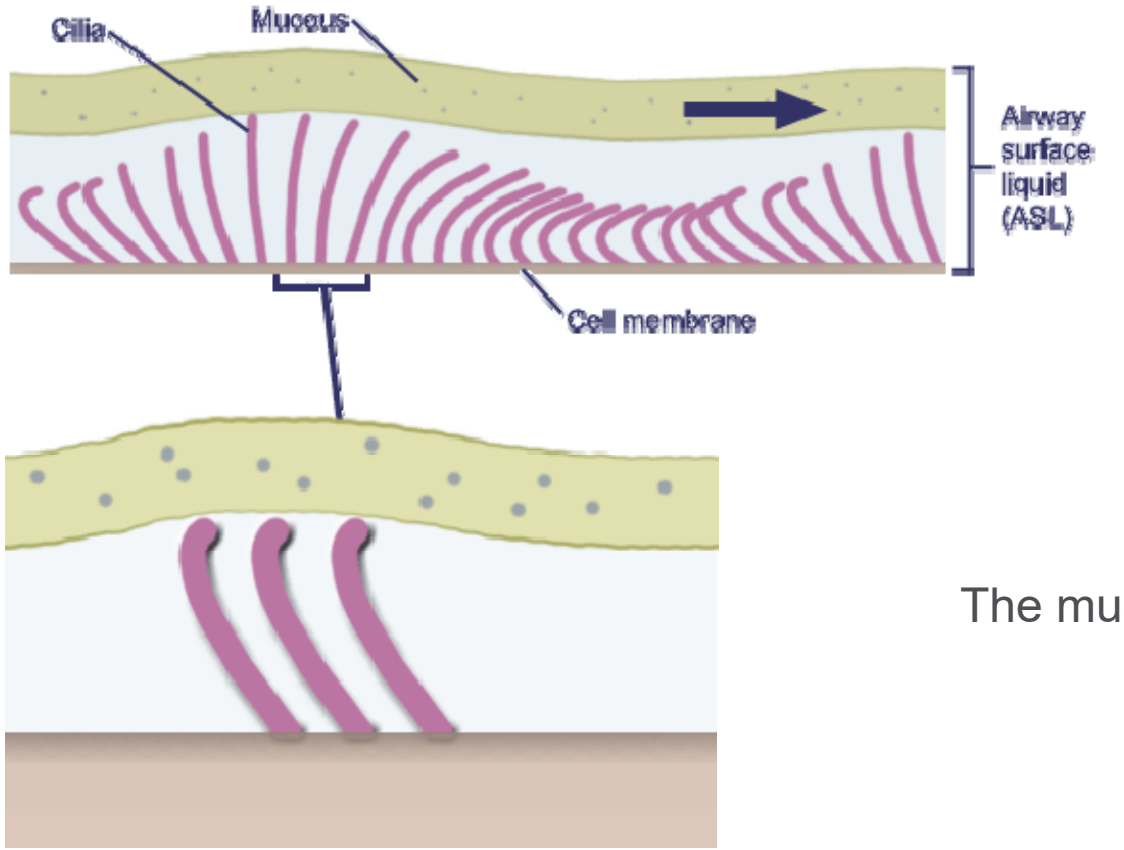
Functions of healthy airways



The mucociliary escalator

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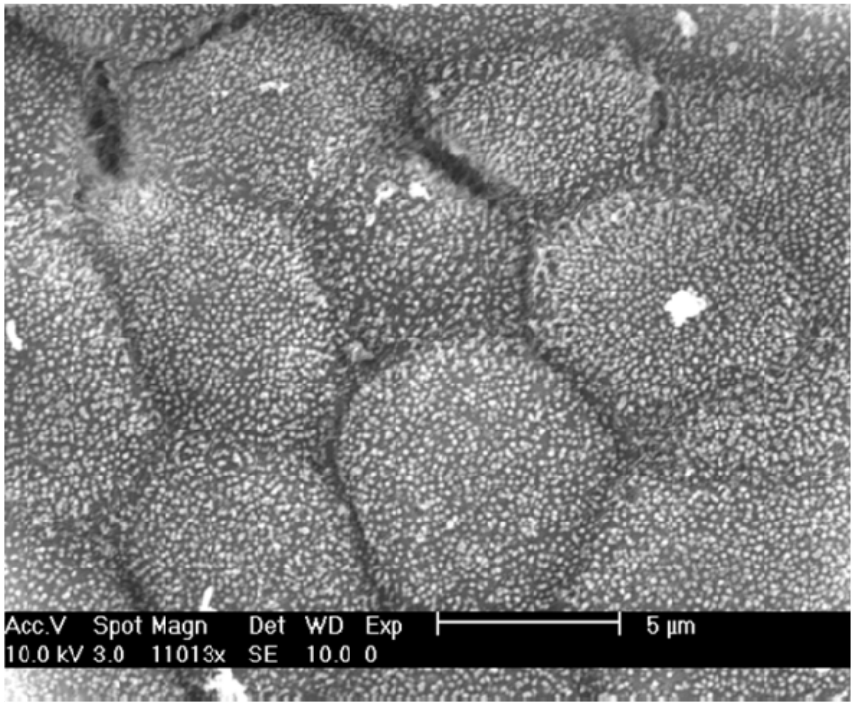
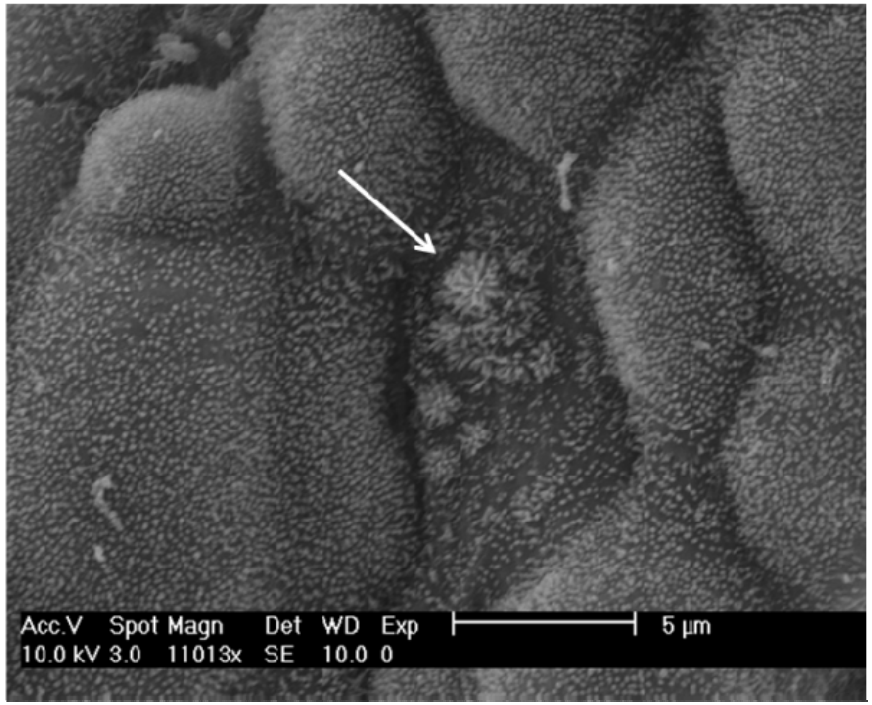
Taken from http://leavingbio.net/Respiratory%20System/THE%20RESPIRATORY%20SYSTEM_files/image012.gif

ALI promotes the production of cilia…





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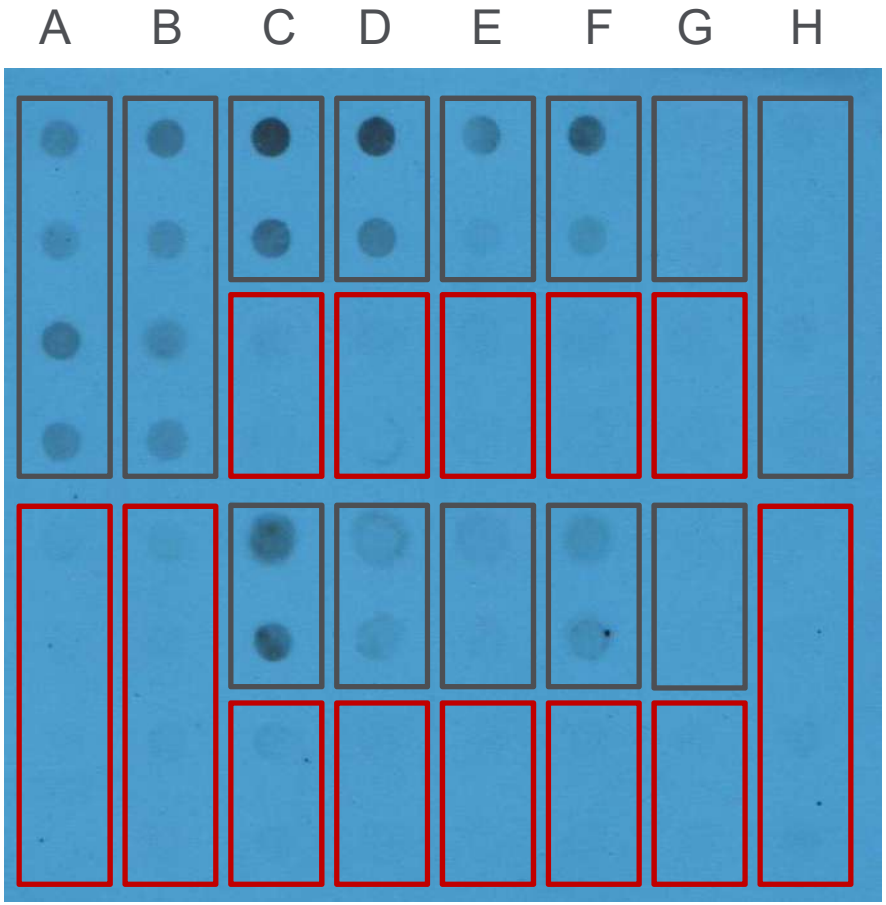
… and mucus secretion



A= Non CF co-culture

B= CF co-culture

C and F = CF mono-culture

D and E= Non-CF mono-culture

G= Submerged epithelial mono-cultures

H = HPF mono-culture

Black boxes indicate apical supernatants
Red boxes indicate basal supernatants

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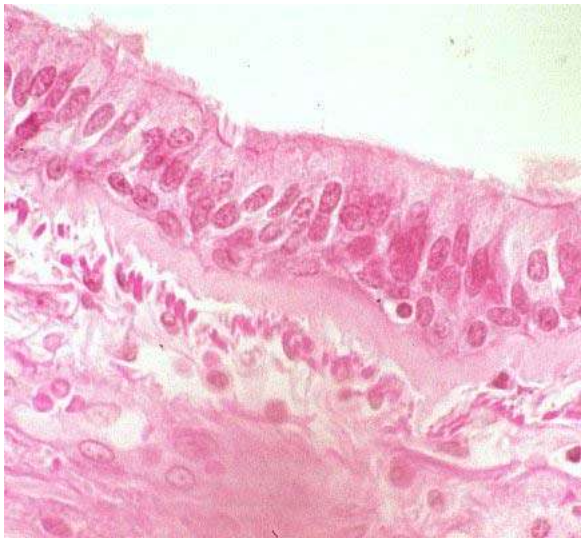
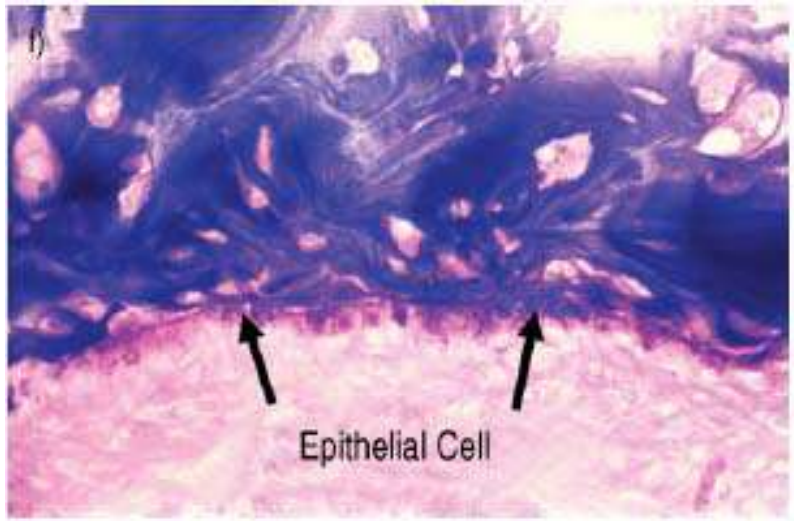
Modelling in sickness: airways disease

Non-CF airway epithelium



CF airway epithelium



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CF airways disease

CF = Defective CFTR

↓

Colonisation by pathogens (particularly *Pseudomonas aeruginosa*)

↓

Chronic inflammation

↓

Epithelial cells release danger signals

↓

These signals attract high numbers of neutrophils

↓

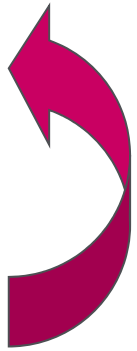
Neutrophils release enzymes

↓

Enzymes damage the airway tissues

↓

Bronchiectasis, narrowing of the airways and eventually death



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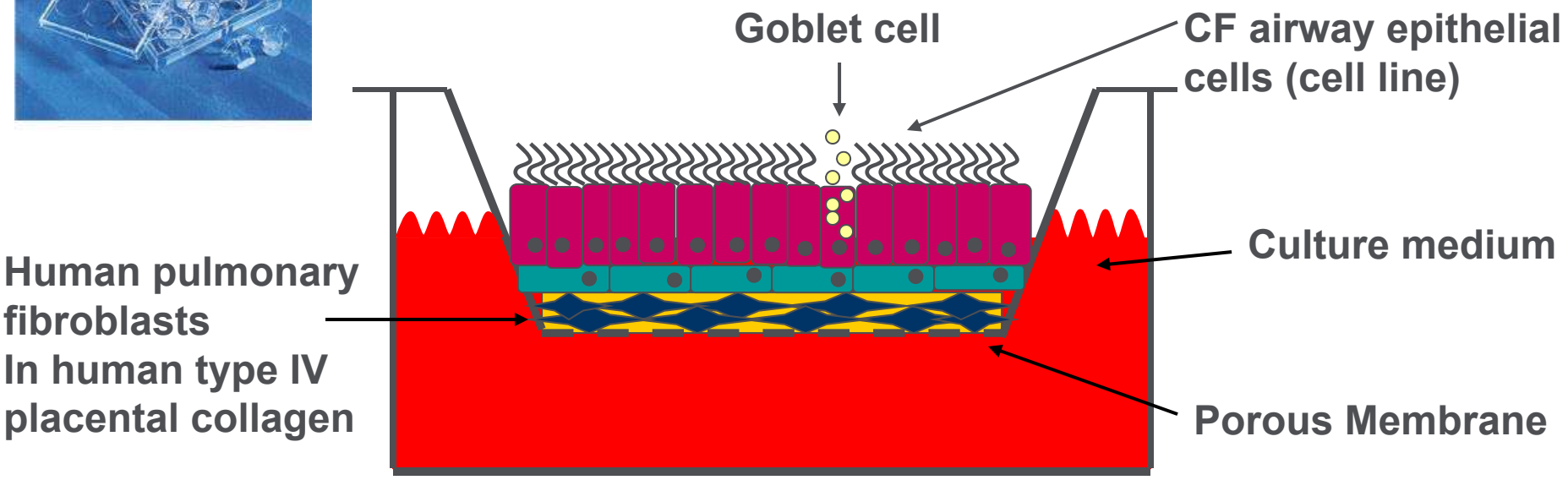
Aston's co-culture model of sick human airways



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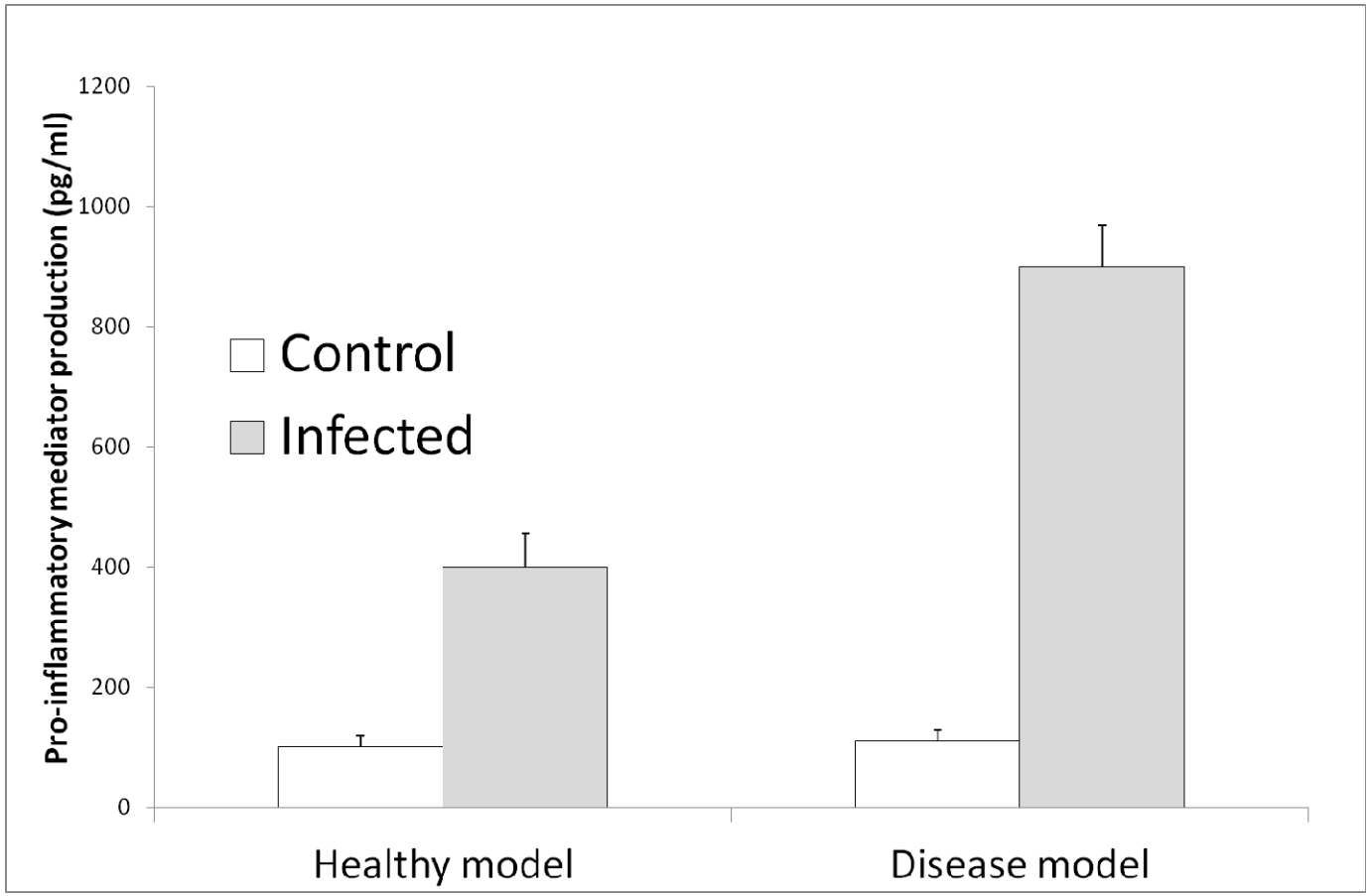
The sick model resembles the human condition: 1. A hyperinflammatory response



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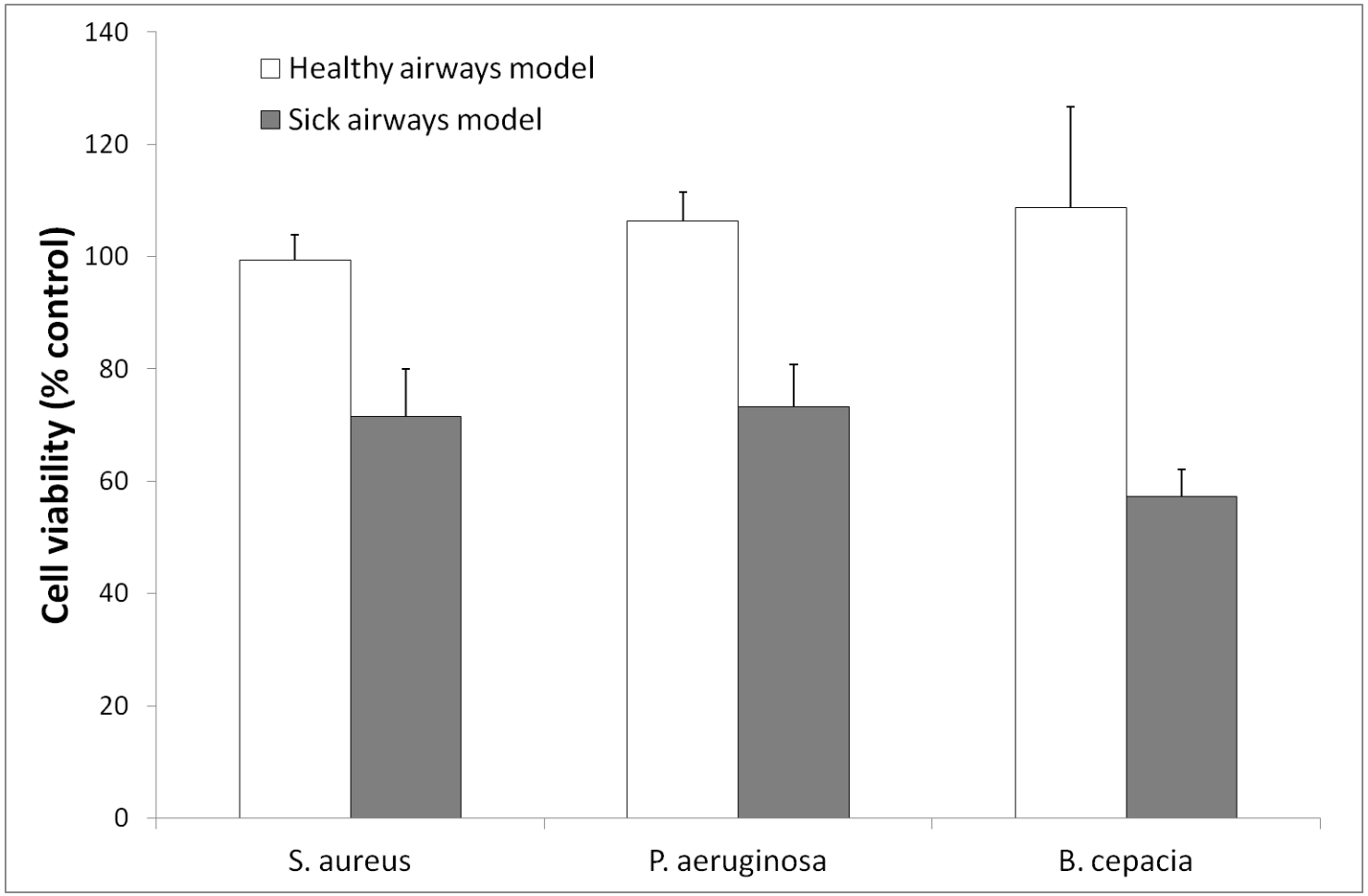
The sick model resembles the human condition: 2. Susceptibility to pathogens



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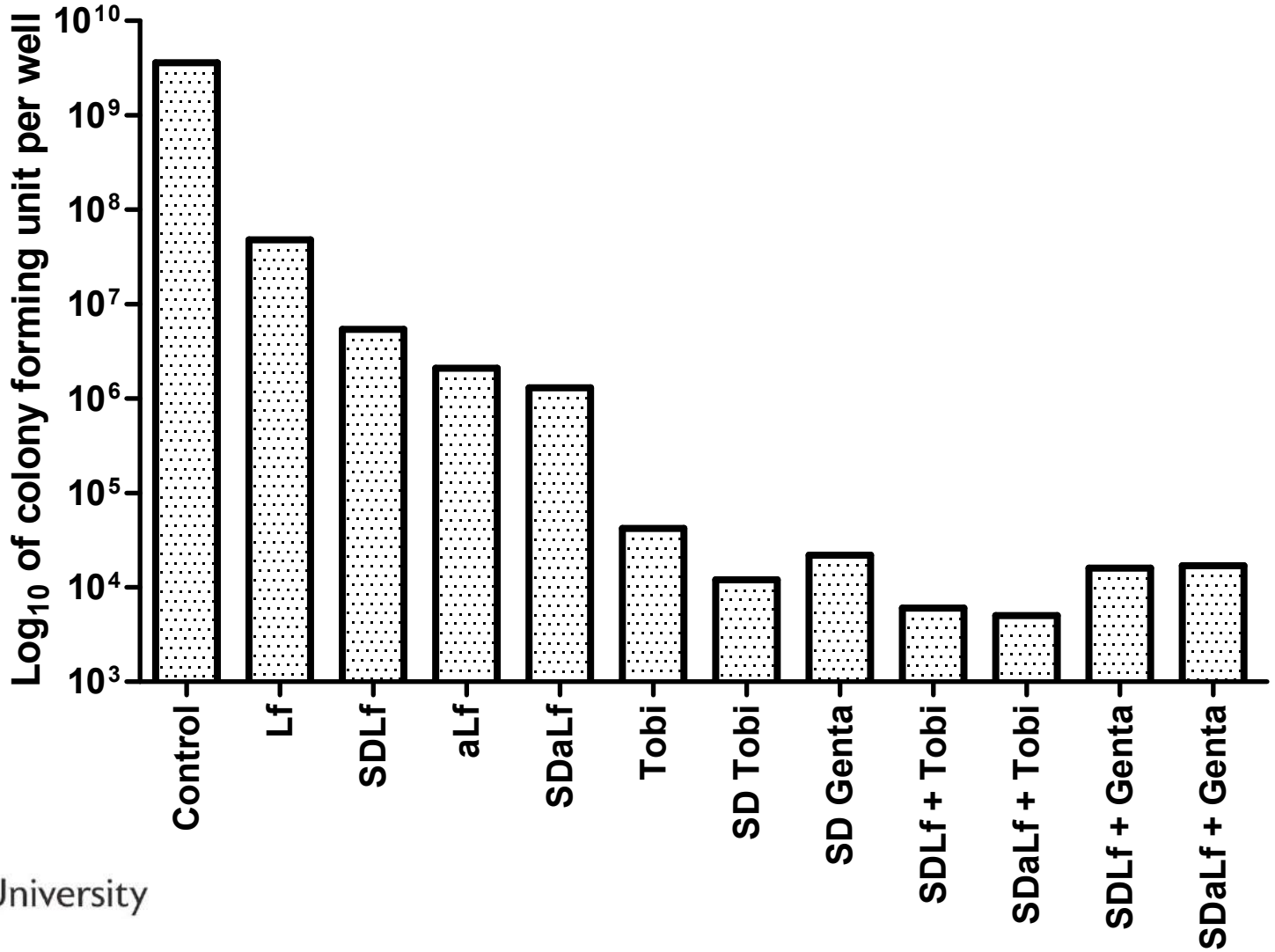
Potential treatments are effective in our models



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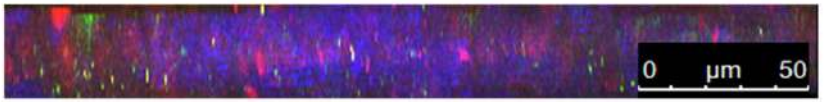
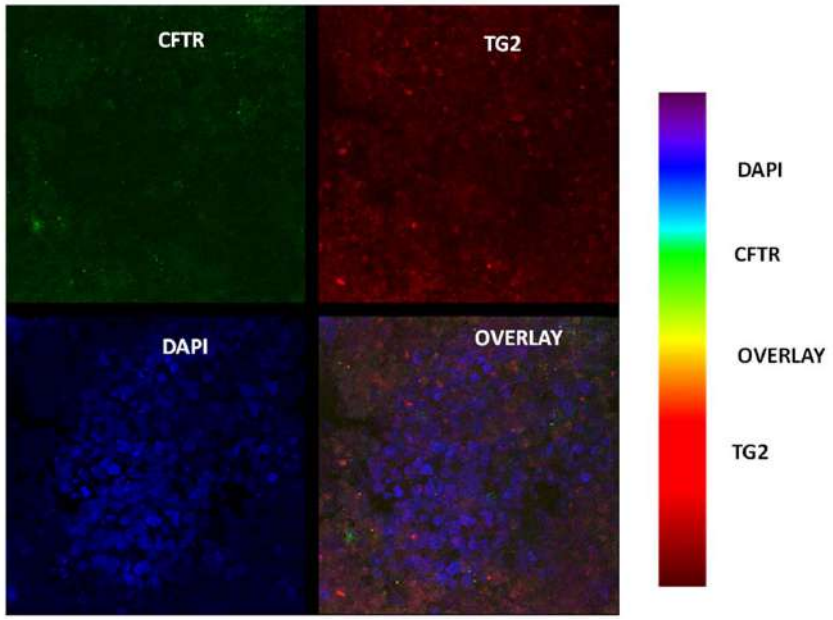
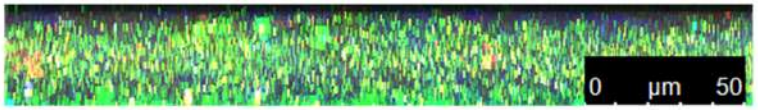
Current treatments are effective in our models

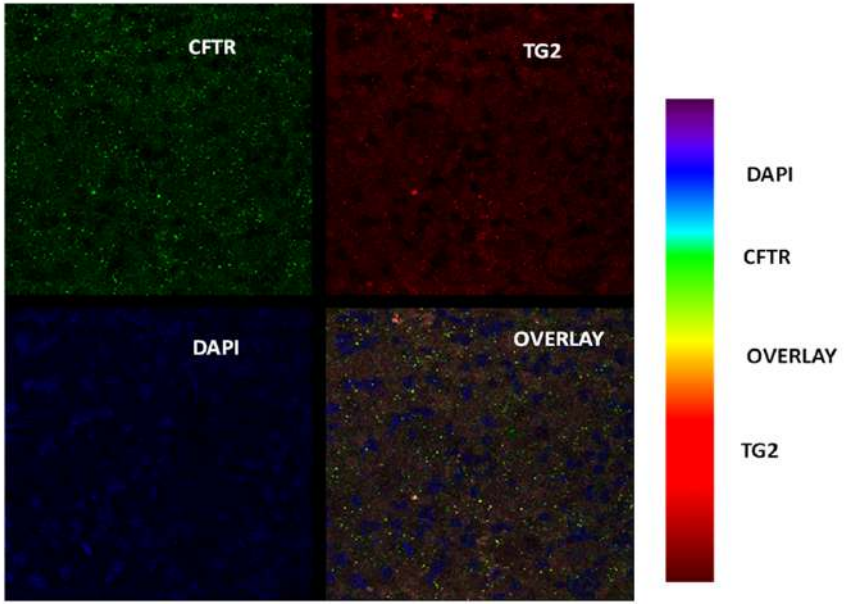
Cross section IB3 cells showing TG2 and CFTR expression in cells cultured at ALI.





Cross section IB3 cells showing TG2 and CFTR expression in cells cultured at ALI and treated with CFTR corrector, VX809.





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Do we have a useful model?

- We are very close and have many features of a useful model:
- Healthy airways -
- Human cells - morphology, phenotype and function
  - To improve this: tissue from nasal/bronchial brushings, lung resection, transplant material

- Sick airways -
- Appropriate pathogens (clinical isolates)
- Therapeutic strategies
  - Model inhaled infections/therapies
  - Expose cells to aerosols
- Work in progress- watch this space…

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Acknowledgements

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