In vitro biopharmaceutical characterisation of nasal products
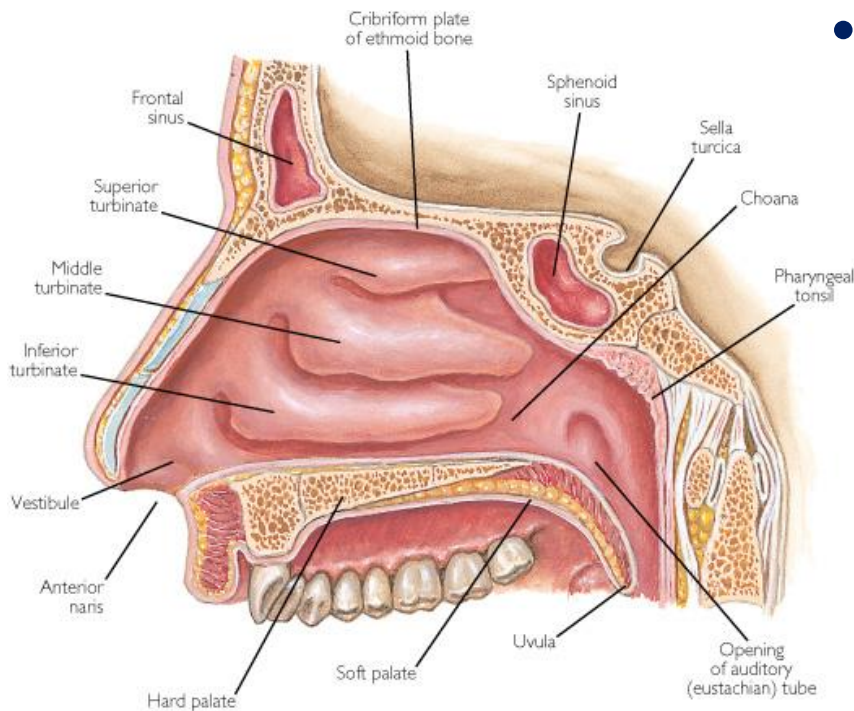
APS Workshop at DDL 2022
December 7th 2022

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Principal Lecturer in Pharmaceutics

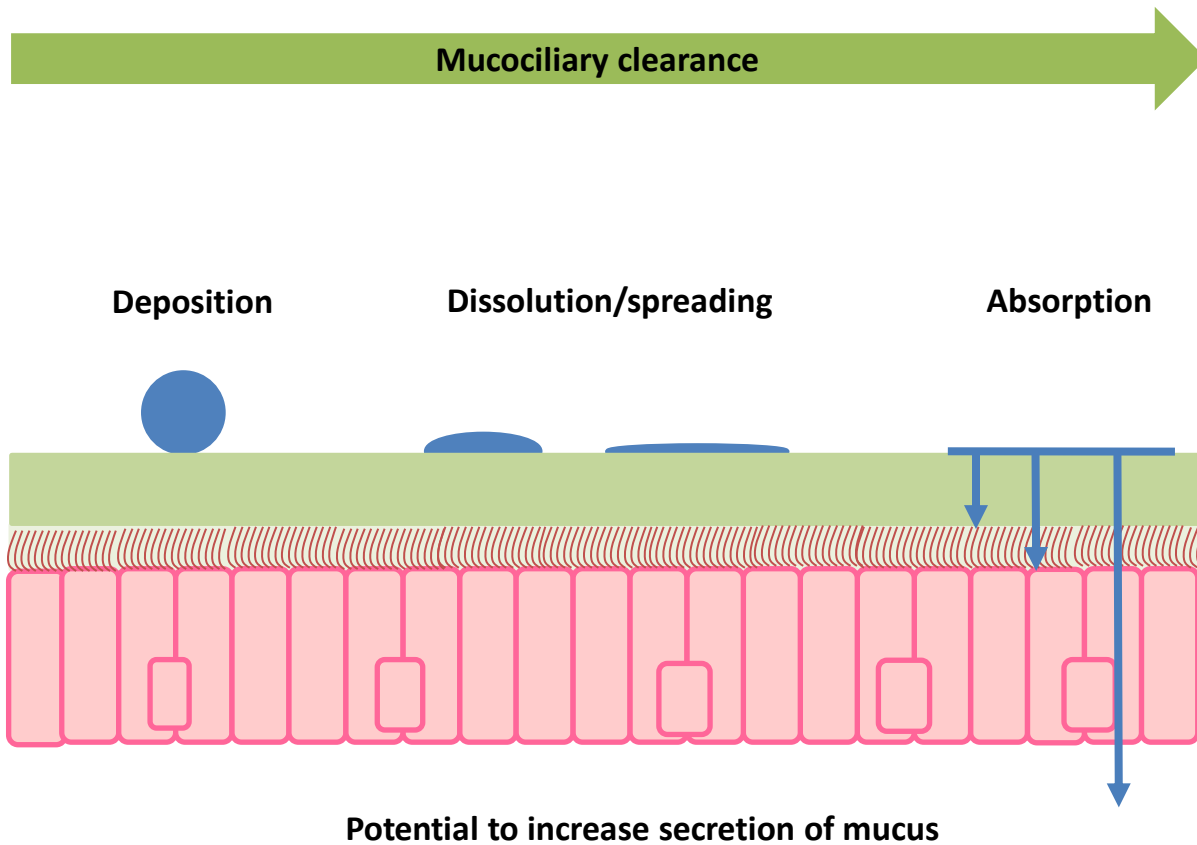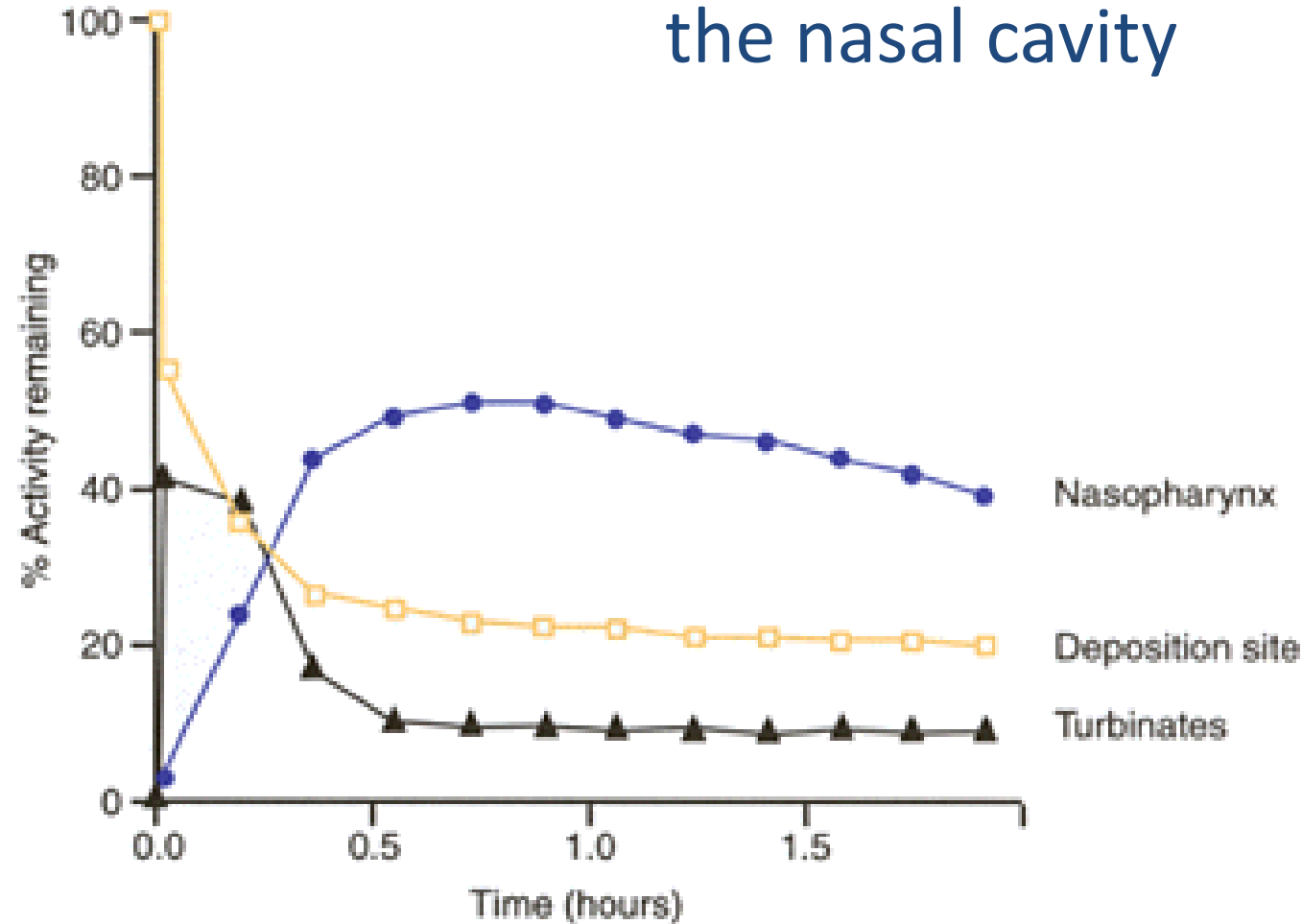**University of Brighton**

What regions do we want to model?

- **Different areas of nasal cavity**
  - Turbinates (~150 cm^2)
    - Submucosal glands, goblet cells
  - Olfactory region (~10 cm^2)
    - Bowman's glands
  - Nasal-associated lymphoid tissue (NALT); Waldeyer's ring (tonsils)

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Mucociliary clearance

Deposition   Dissolution/spreading   Absorption

Potential to increase secretion of mucus
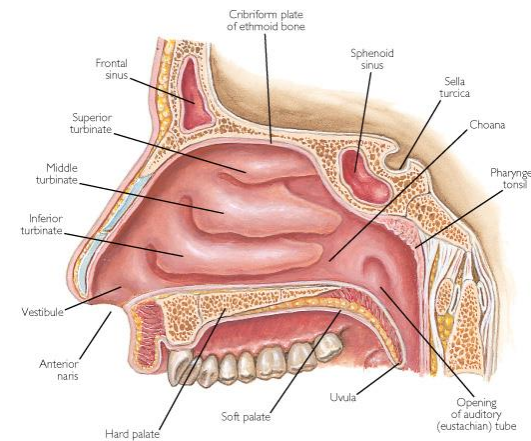
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Deposition and clearance of a nasal spray from the nasal cavity

Bulk cleared from turbinates
after 20 minutes

Complete recapitulation of native tissue or just key (rate-limiting) features?
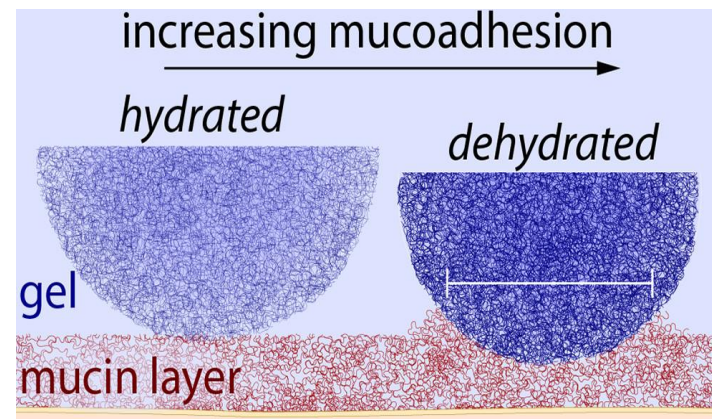
- Mucus

- Mucociliary clearance
    - Is this necessary for drugs in solution?
    - Could it be controlled for by exposure time?

- Barrier provided by epithelium
    - Appropriate TEER
    - Relevant transporters

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Role of mucus in drug delivery is often neglected
Involved in:

- ## Dissolution
  - Drugs in suspension
  - Soluble fillers

- ## Swelling of polymers
  - Competition with mucin for water
  - Mucoadhesion

McGhee, E. O. et al. *Langmuir* **2019** *35* (48), 15769-15775

Role of mucus in drug delivery is often neglected Involved in:

- Diffusion barrier/binding

- Biocompatibility
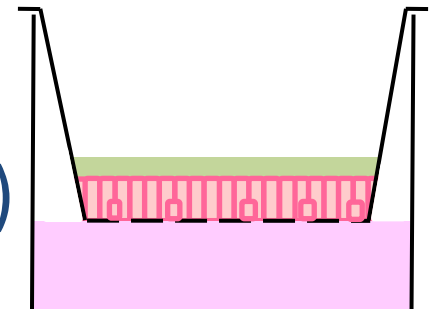 - Increased mucus secretion

Models used to consider role of mucus

- Native mucus
- Mucin solutions
- Mucus or artificial mucus applied to cells that don't secret mucus
- **Mucus-secreting cell lines**
- Co-cultures of mucus-secreting cells and cells that don't secrete mucus
- Primary cell cultures
- Explants
- *Ex vivo* tissue
    - Olfactory mucosa; Waldeyer's ring (tonsils, adenoids, and other lymphoid tissue)
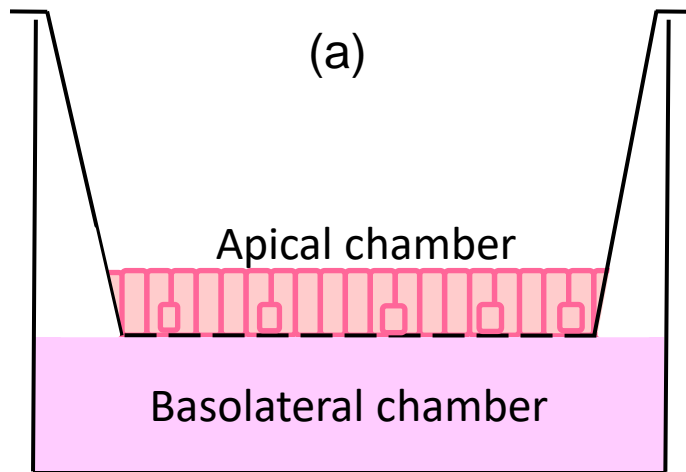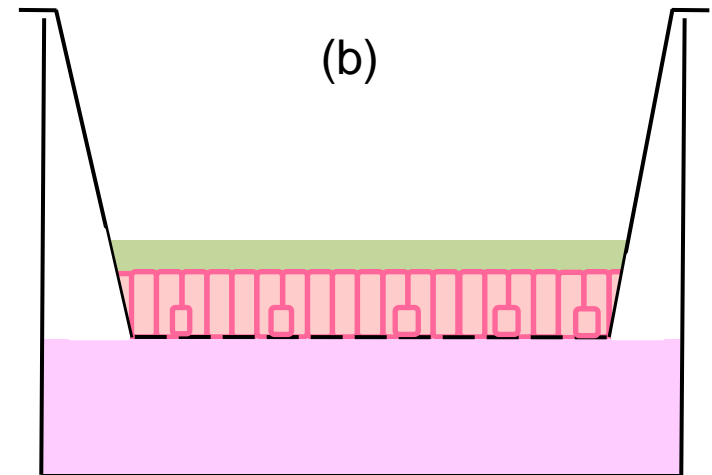
Cell models of turbinates that secrete mucus

- Human lung cell line (Calu-3)
- Rat tracheal cell line (SPOC-1)
- Human bronchial cell line (UNCN3T)
- Human airway epithelial cell line (NuLi-1)
- Human **nasal** epithelial cell line (RPMI 2560)

- Primary cultures of rat, human nasal/airway epithelium (MucilAir, EpiAirway)
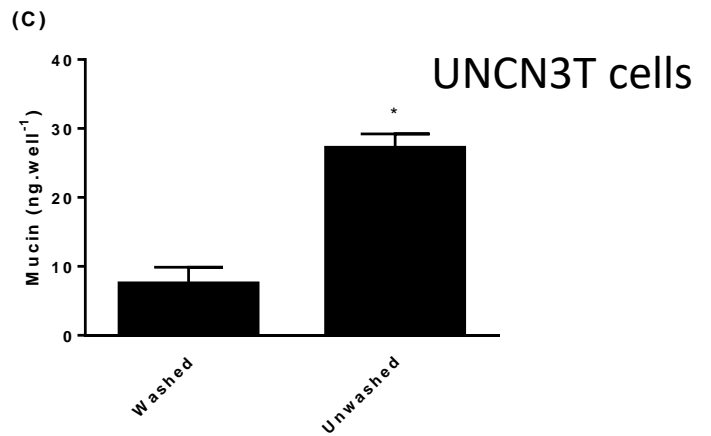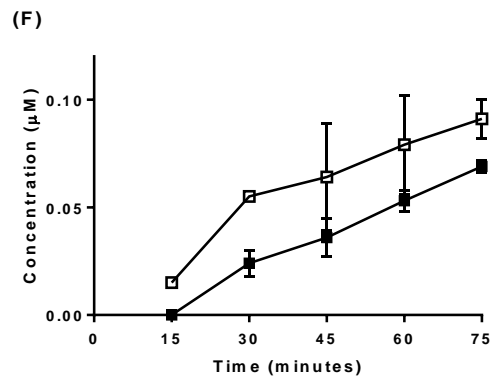
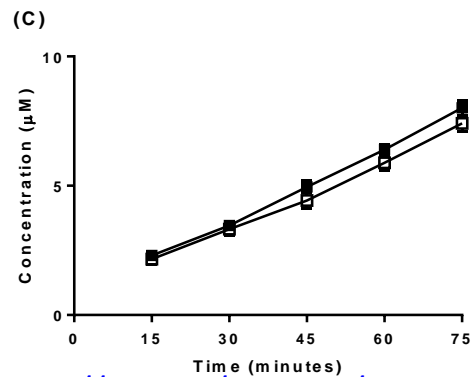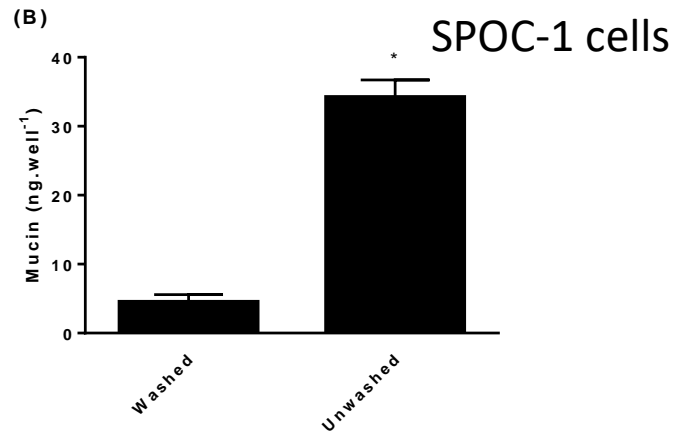- **Goblet cells** (no glandular contribution)

Comparing absorption in absence and presence of mucus

(a)

Apical chamber

Basolateral chamber

Deplete mucus by washing

(b)

Unwashed

(A) FD4

(D) Testosterone

(A) Mucin secretion

Calu-3 cells

(B)

(E)

(B) SPOC-1 cells

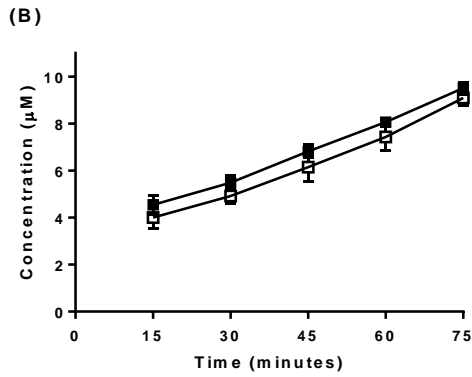**(C)**

(F)

(C) UNCN3T cells

https://doi.org/10.1016/j.ejpb.2021.07.016
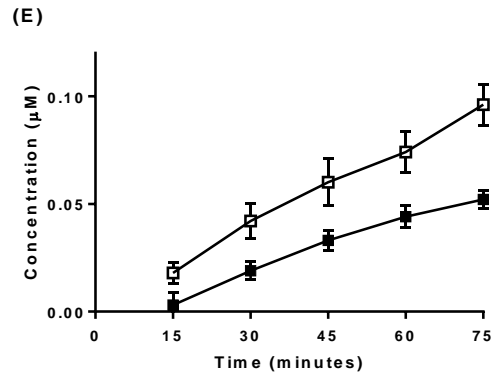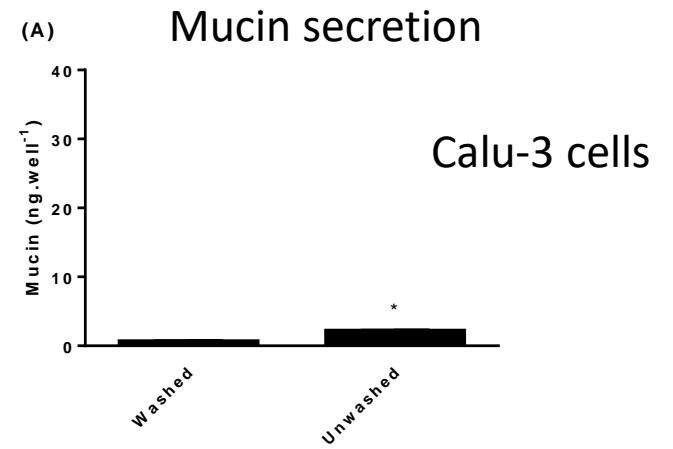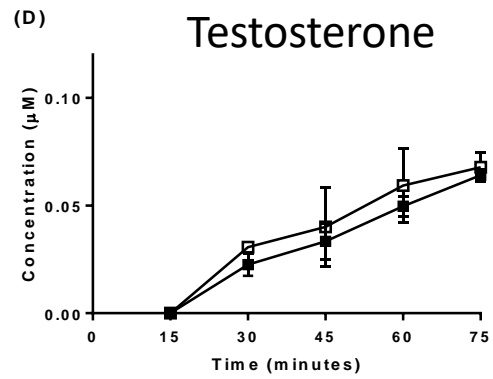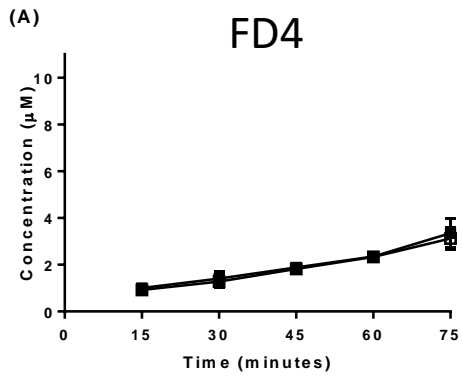
Validation of cell models

- Standard culturing conditions

- Standard experimental protocol

- Standard set of compounds with a range of physicochemical characteristics to test/validate each model

Validation of cell models

- Ideally, *in vitro - in vivo* correlation in human (rather than rodents)
  - Drug in blood (or urine) at 30 min (*cf*. lung) or earlier
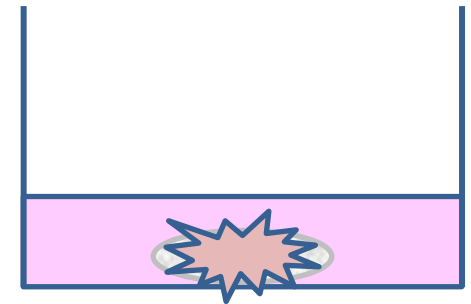 - Aerodynamic droplet/particle size controlled to avoid lung deposition

- What is deposition area of delivery device? – link to area of cells?

- What is retention time in nasal cavity – link to duration of experiment?

Ovine tracheal epithelial explant showing ciliated cells and goblet cells

Goblet cells

Ciliated cells
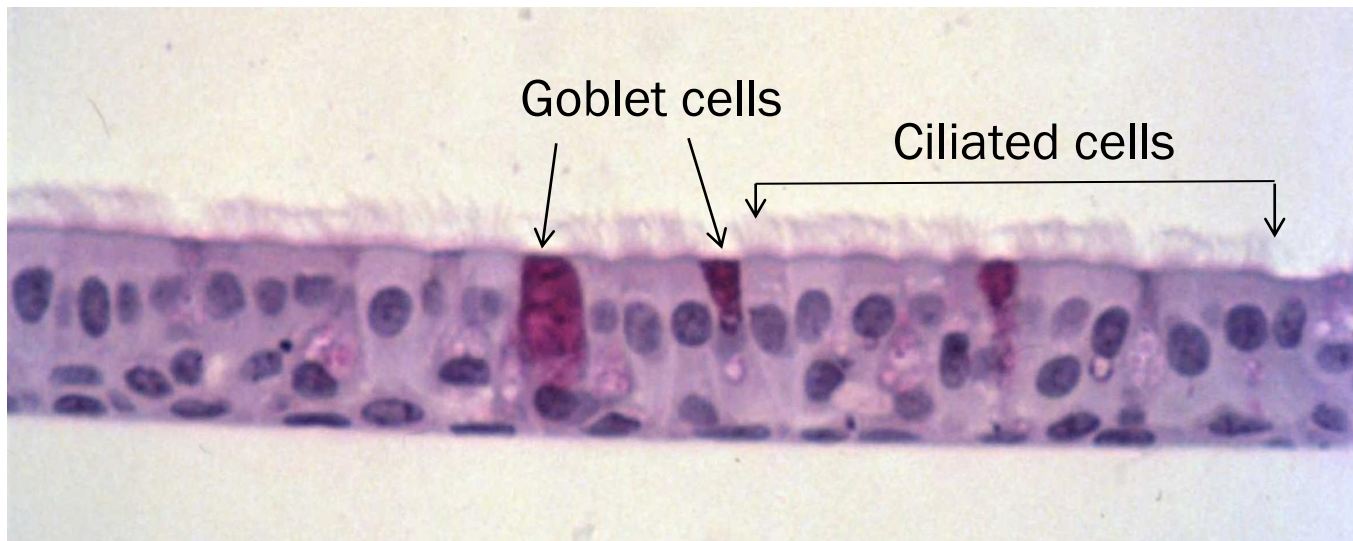
Biocompatibility

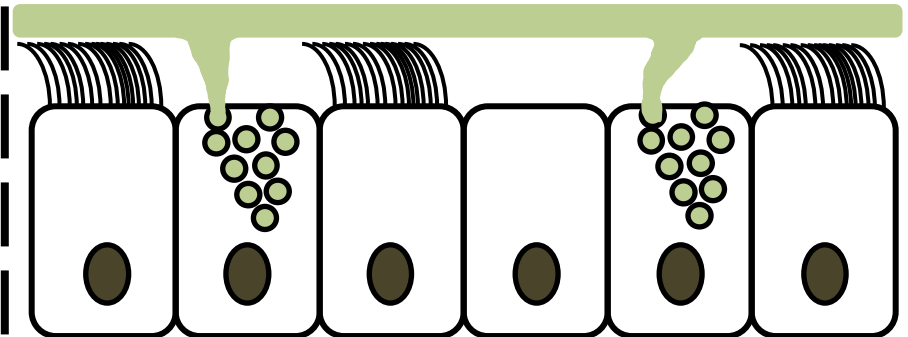Benzalkonium chloride (0.015% w/w)
Methocel™ E50 premium LV (1.0% w/w)
Propylene glycol (PG) (1.5% w/w)
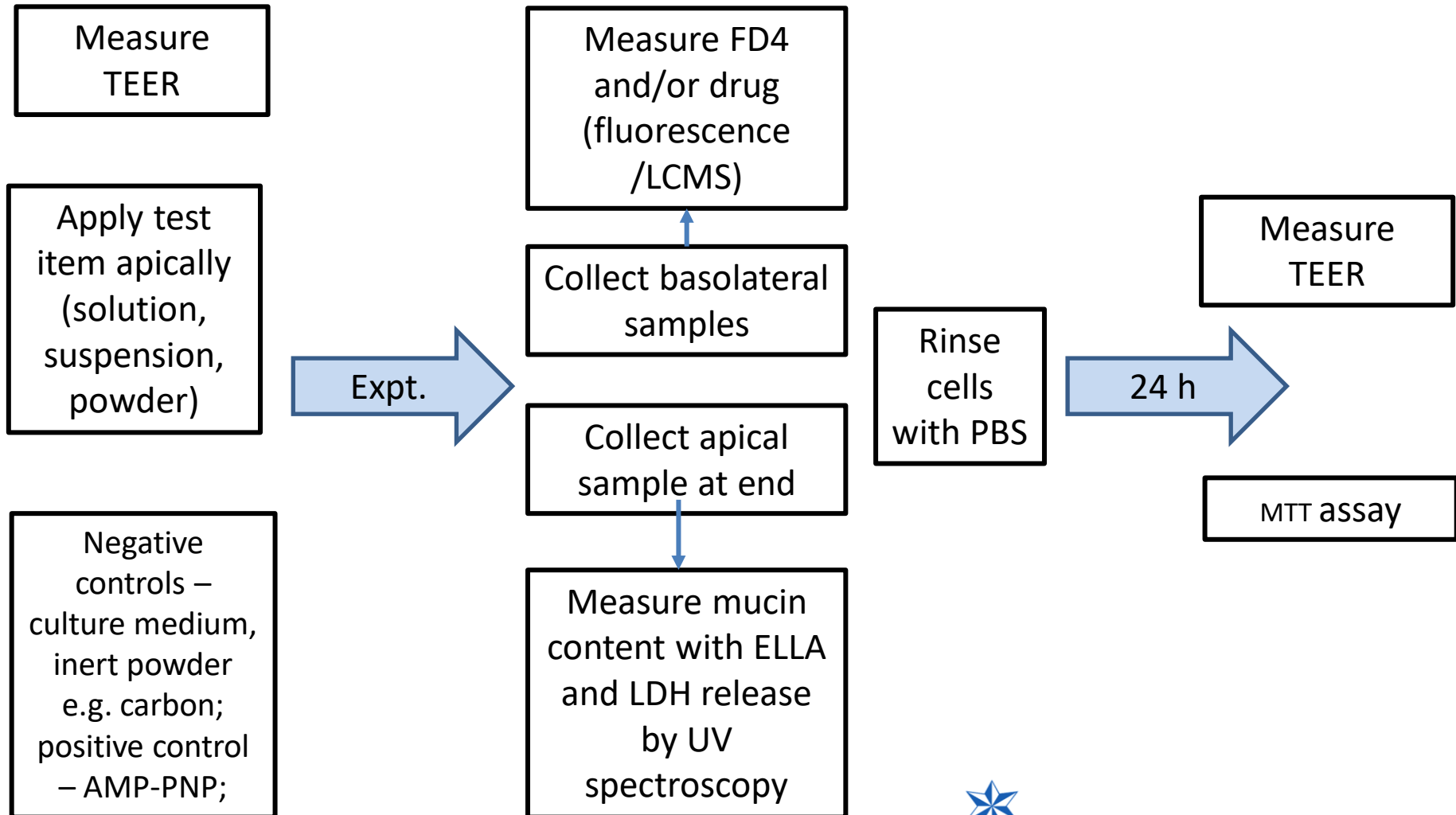Potassium sorbate + PG (0.3% w/w + 1.5% w/w)
Polysorbate 80 (0.025% w/w)

EDTA (0.015% w/w)
Avicel® RC591 (1.5% w/w)
Fluticasone furoate *in solution* (0.0004% w/w)
DMSO (0.2% w/w)

Increased mucin secretion

Did not affect mucin secretion

Absorption and biocompatibility

Measure TEER

Apply test item apically (solution, suspension, powder)

Negative controls – culture medium, inert powder e.g. carbon; positive control – AMP-PNP;

Expt.

Measure FD4 and/or drug (fluorescence /LCMS)

Collect basolateral samples

Collect apical sample at end

Measure mucin content with ELLA and LDH release by UV spectroscopy

Rinse cells with PBS

24 h

Measure TEER

MTT assay

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- Dr Mike Lethem

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Questions

- What regions of nasal cavity do we want to model?

- Complete recapitulation of native tissue or just key (rate-limiting?) features?

- How important is mucus in nasal drug delivery?

- How best to validate existing/new models?