UNIVERSITÀ DEGLI STUDI DI TORINO

POLITECNICO MILANO 1863

UNIVERSITÀ DI PAVIA

May 27
2021

ECBS 2021
EUCHEMS / EU-OPENSCREEN

Understanding the mechanisms governing the interaction of drugs with mucus using a novel biosimilar mucus model

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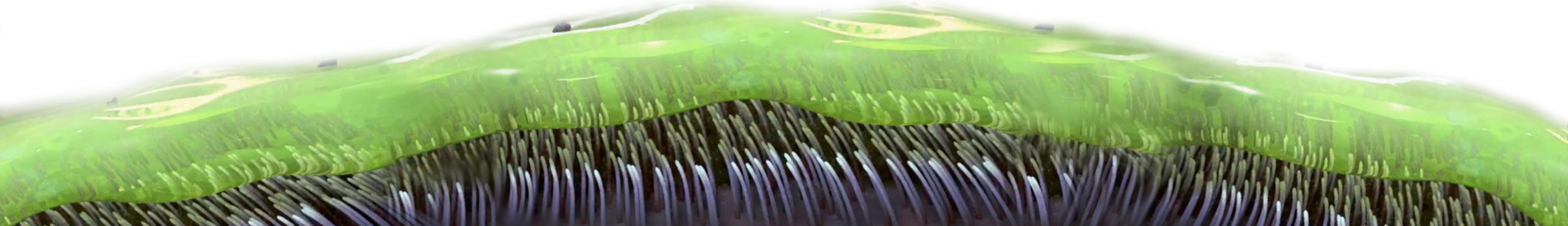
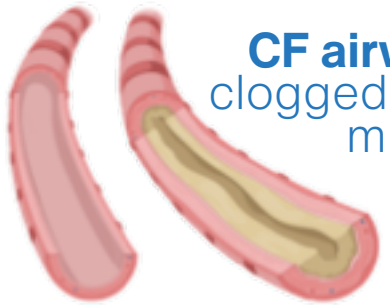


Introduction | mucus is a multifaced barrier

Mucus is the **body's first line of defense**

Disorders associated with mucus overproduction

- Cystic fibrosis
- COPD
- Asthma



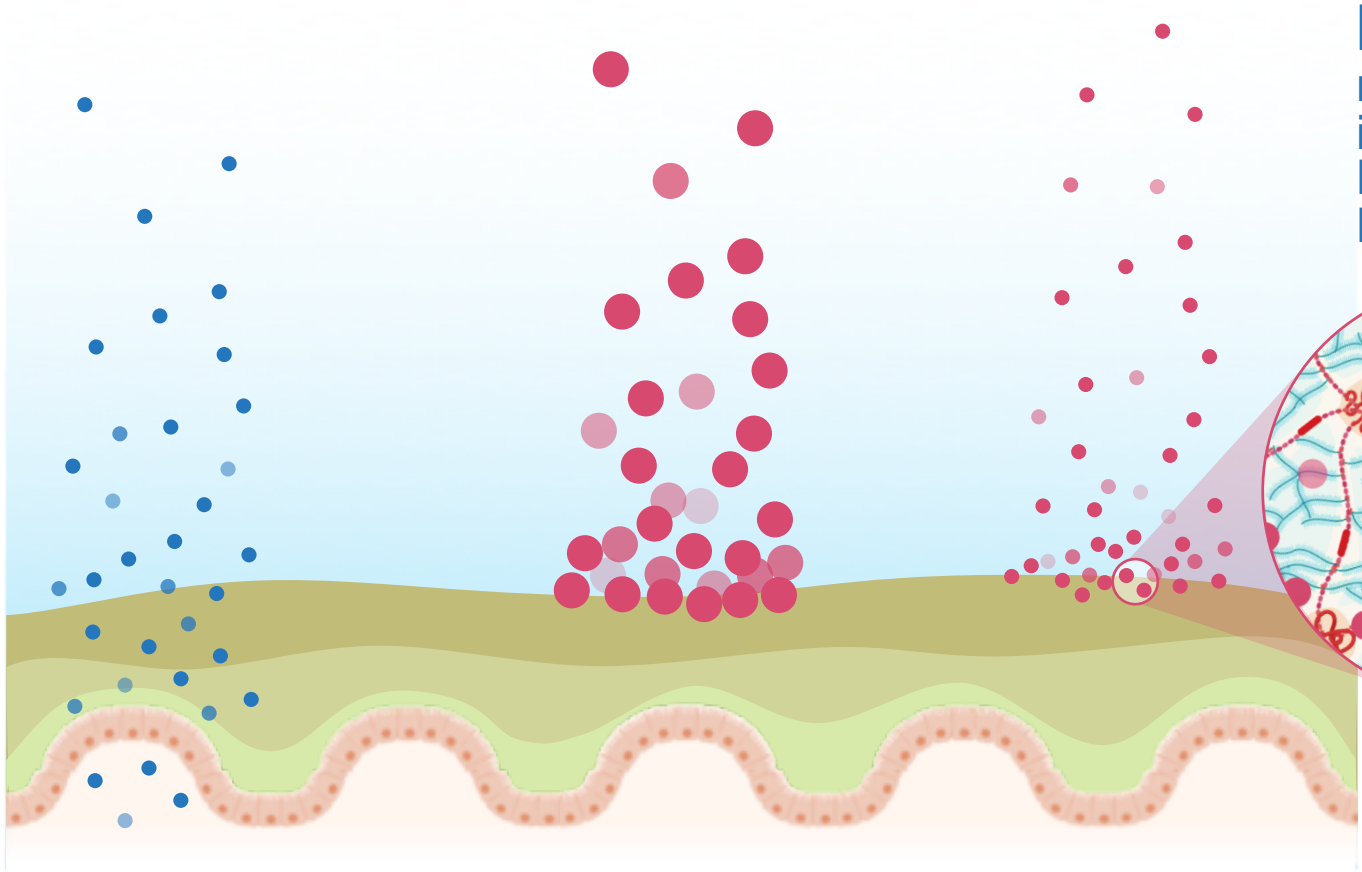
CF airways clogged with mucus

Normal Cystic fibrosis

Free diffusion

Steric Barrier
(Mesh size 20-1800 nm[1])

Interactive barrier



Drugs may rest trapped into the **mucus network**

[1] Leal J., et al., Int. J. Pharm, Vol. 532, (2017), 136-144, DOI 10.1016/j.ijpharm.2017.09.018

The solution | a biosimilar mucus model

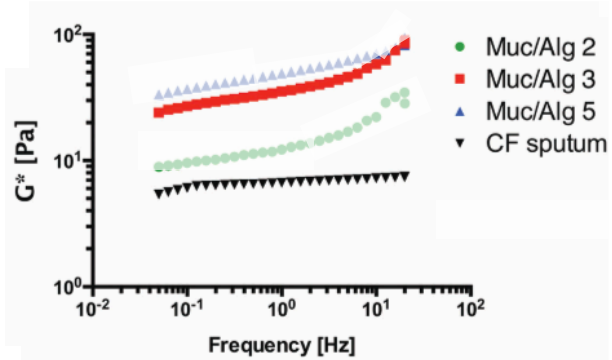
What we need

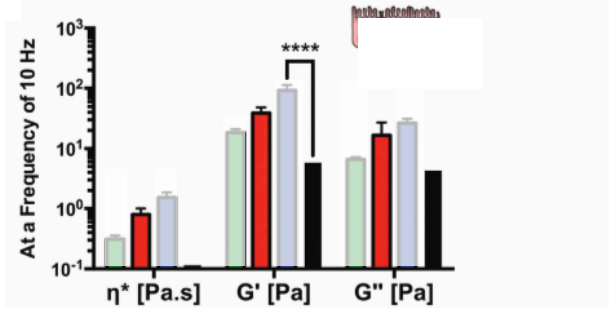
Realistic 3D *in vitro* mucus model

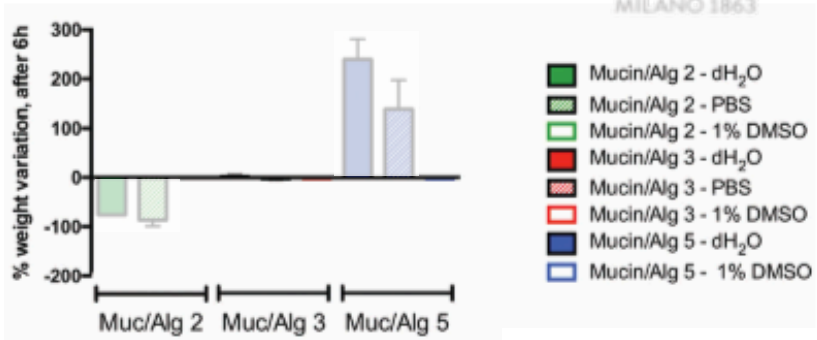
Standardized model suitable for HTS purposes

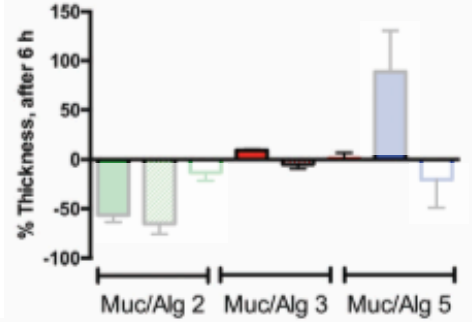
Reduce ineffective drug candidates

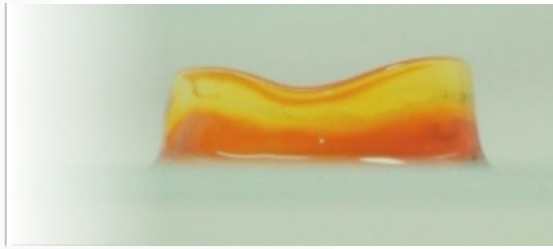
Mucin-alginate based **airway mucus** model that reproduces the chemical-physical **properties of CF mucus**







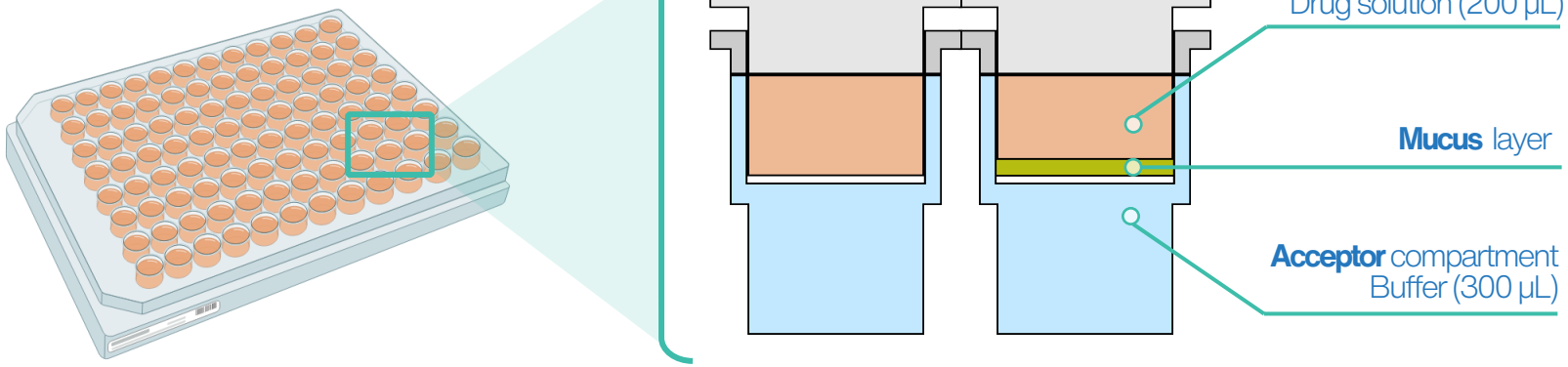




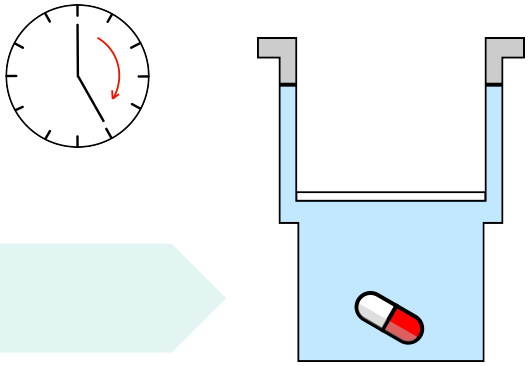
[1] D. Pacheco *et al.*, J. Mater. Chem. B, 2019, 7, 4940-4952

Methods | drug diffusion

Parallel artificial membrane permeability assay[2]



Description of **passive diffusion**



LC-MS quantification

Apparent permeability

Flow rate of compound into the acceptor compartment, normalized by surface area (A) and driving concentration (C_0).

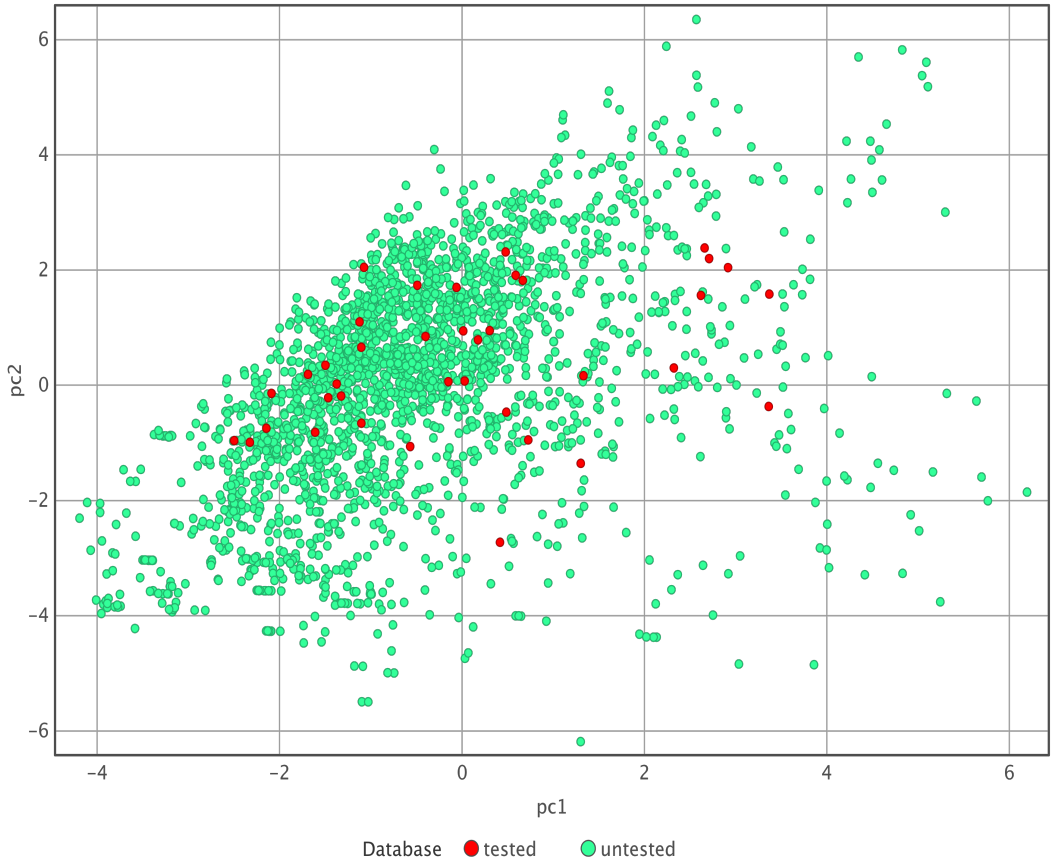
$$P_{app} = \frac{dQ/dt}{C_0 \times A}$$

[2] Kansy., et al., J. Med. Chem, 1998, 41, 7, 1007-1010

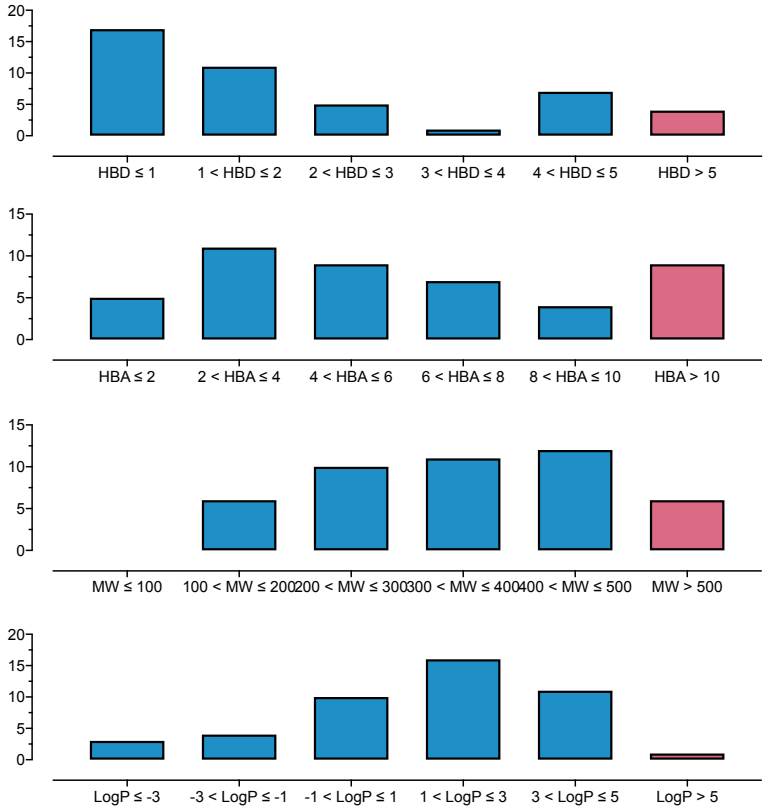
Methods | drug selection

45 commercially available compounds have been tested

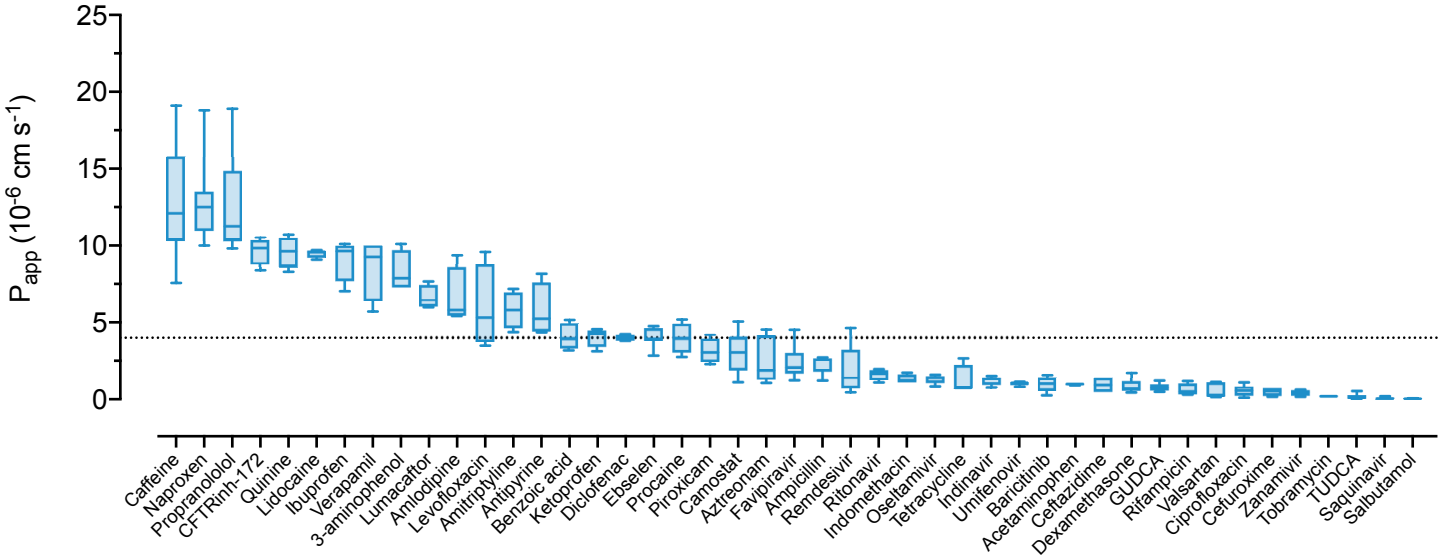
Distribution of the selected compounds within **DrugBank's** approved drugs database

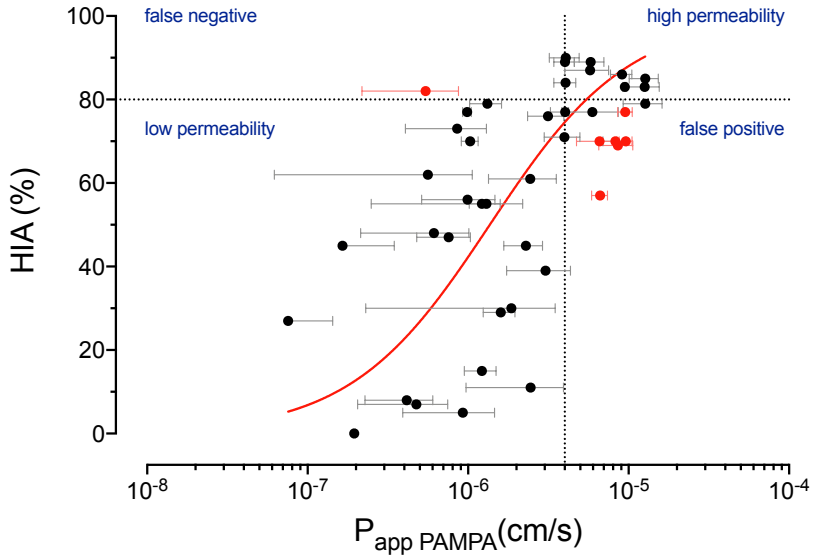


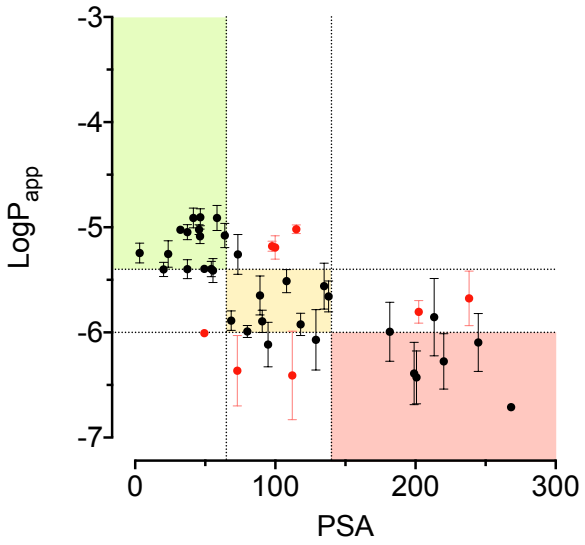
Distribution and classification of the selected compounds within **Lipinski's rule of 5**



Results | drug diffusion on PAMPA







Classification in

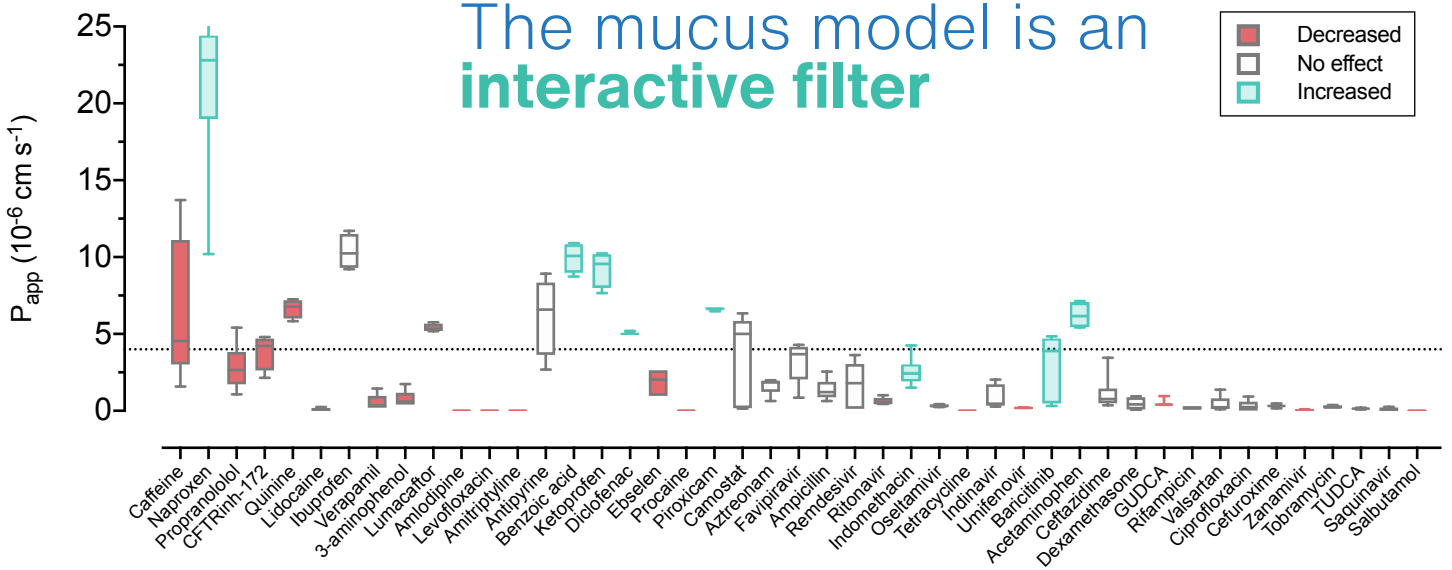
- **High permeable** ($P_{app} \geq 4 \cdot 10^{-6}$ cm/s)
- **Low permeable** ($P_{app} < 4 \cdot 10^{-6}$ cm/s)

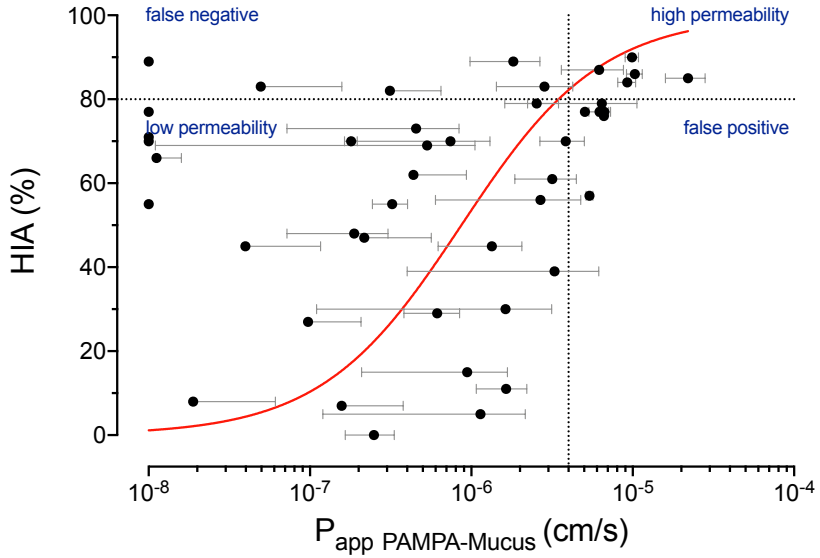
84% of the compounds had the permeability correctly identified based on their Human Intestinal Absorption (HIA)

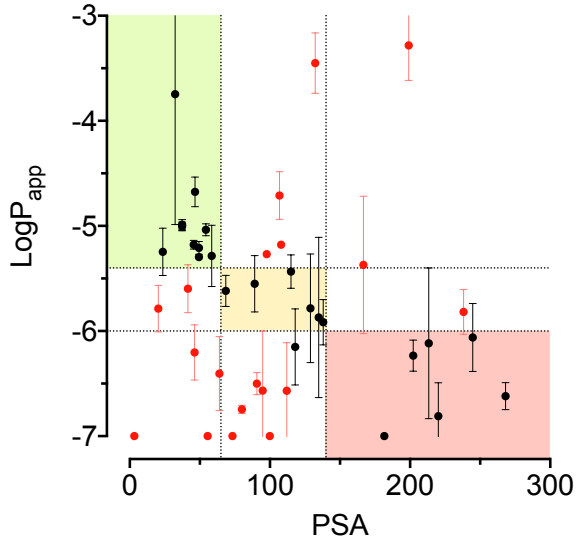
81% of the compounds had the permeability correctly identified based on their Polar Surface Area (PSA)

Results | drug diffusion on PAMPA + Mucus

The mucus model is an **interactive filter**







Heterogeneous effect of mucus on permeability:

- Decreased
- No effect
- Increased (suspect ion-pair)

Increased deviation of permeability from the prediction based on Human Intestinal Absorption (HIA)

57 % of the compounds had the permeability correctly identified based on their Polar Surface Area (PSA)

Conclusions

The effect of mucus is difficult to predict in pathological conditions and the PAMPA system is a too simplistic model

A fast screening of highly retained compounds can be assessed with the herein presented *in vitro* mucus model

Retention within mucus is a complex phenomenon complementary influenced by many molecular descriptors (charge, MW, PSA, LogP...)

Thank you
for your attention!