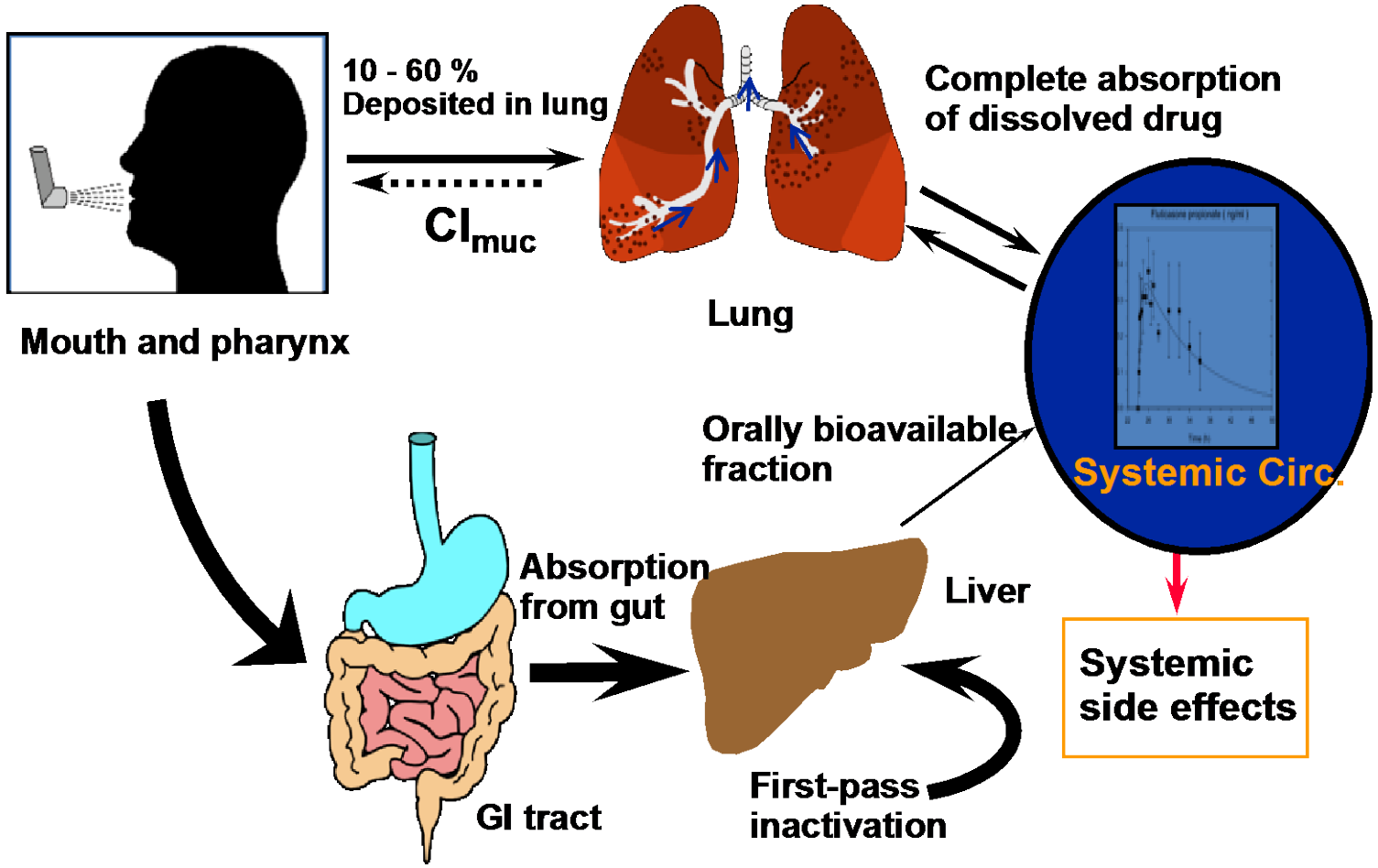
Preclinical Models for Pulmonary Delivery

11/6/2019

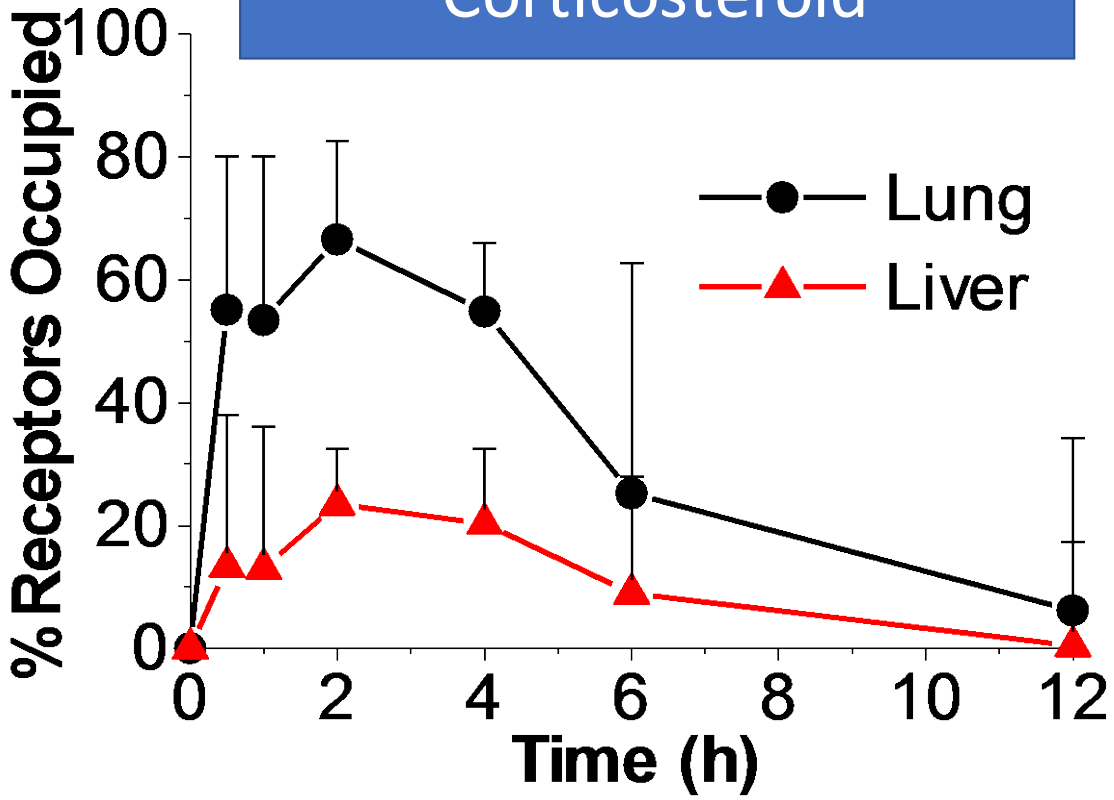
Günther Hochhaus

Pulmonary Delivery is rather Complex



Pulmonary Targeting
In Rat Ex-vivo Receptor Binding Assay

Intratracheal
Corticosteroid



Optimized Characteristics of device/formulation/API for targeted delivery

- Lung Deposition
  - Dose
  - c/p Regional Deposition

→ Device, Formulation (excipients), API (physicochemical properties)

- Post-Deposition: Long pulmonary residence time controlled by either
  - Slow Dissolution rate
  - Low Permeability

→ Formulation (excipients), API (physicochemical properties, e.g. particle size….)

- Systemic PK
  - Pronounced systemic clearance
  - Low oral bioavailability

→ API

Preclinical Models

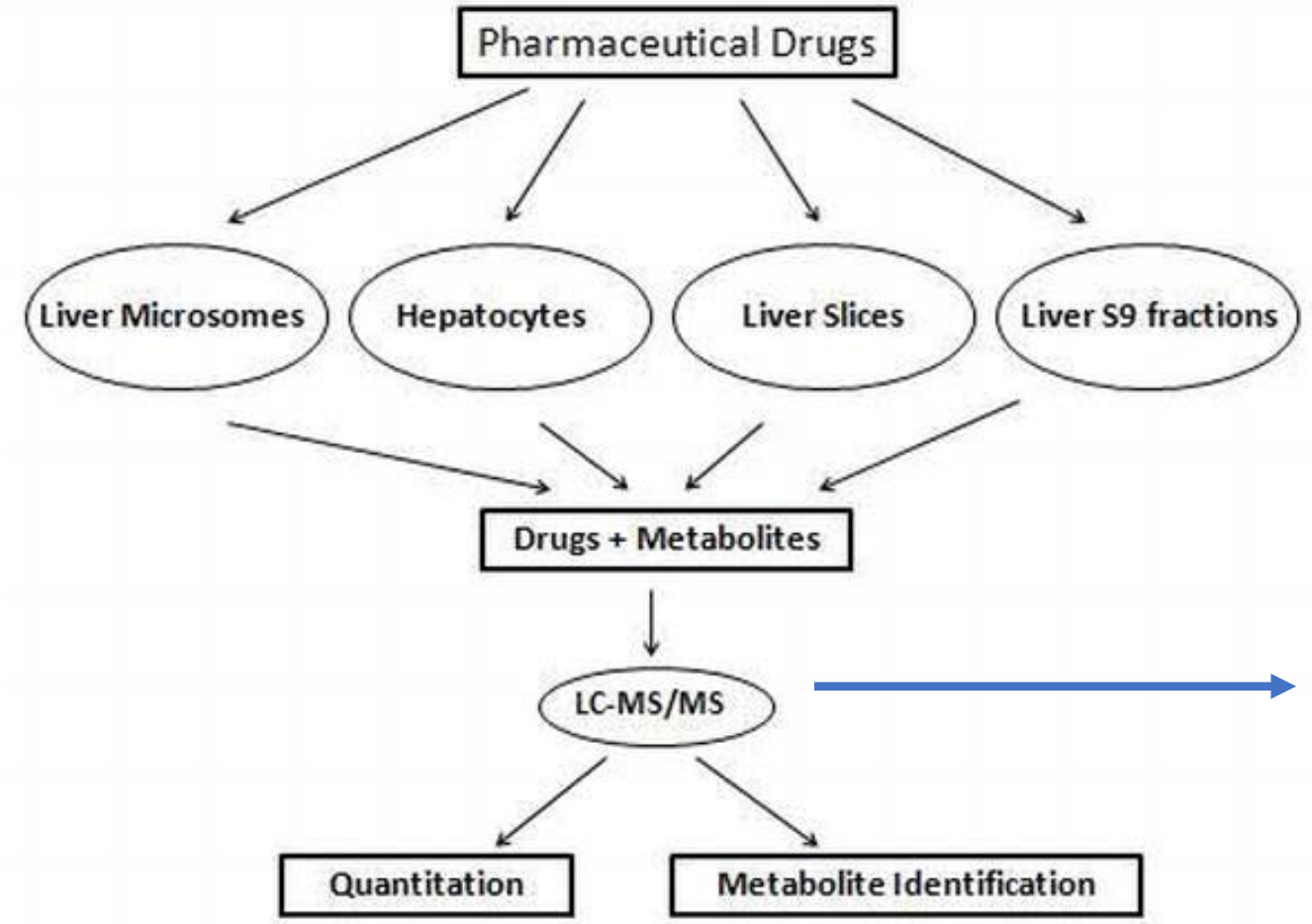
Systemic Fate (Cl, F, protein binding)

- In vitro/cell culture: Clearance/Protein binding/Metabolism
- Animal studies

Pulmonary Fate (Deposition and Post-deposition Events)

- In Vitro (dose, regional deposition; e.g. cascade impactor studies)
- Cell culture (permeability)
- Isolated perfused Lung (dissolution, permeability)
- Animal Studies (rat, dog, sheep, pig,)

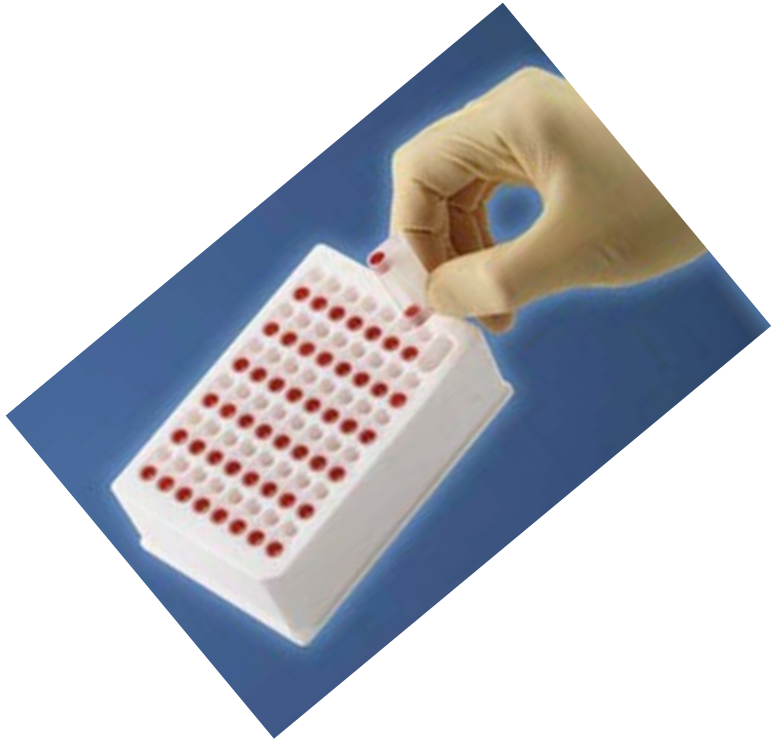
Determination of Cl_{int}

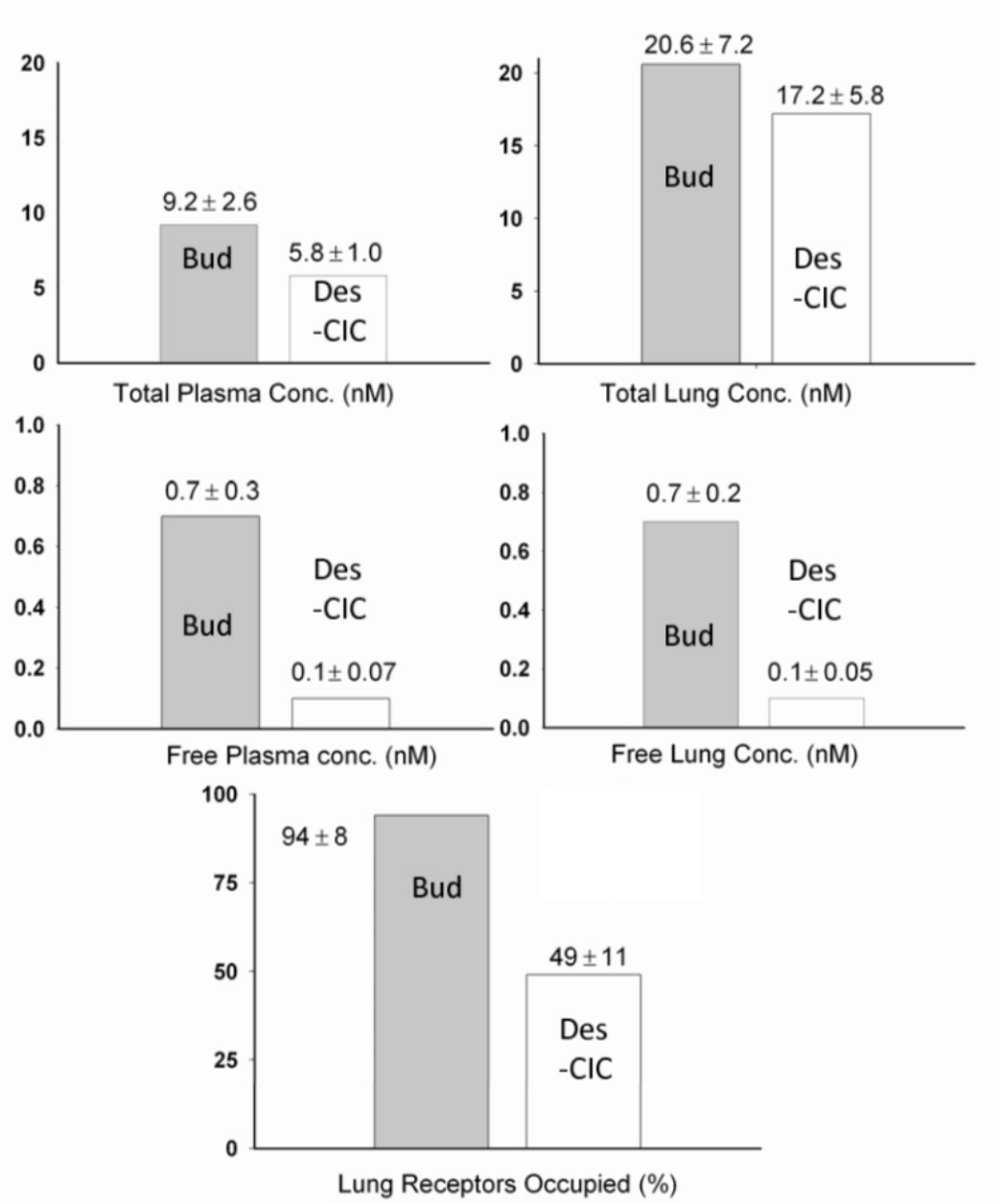


Select NCE with:

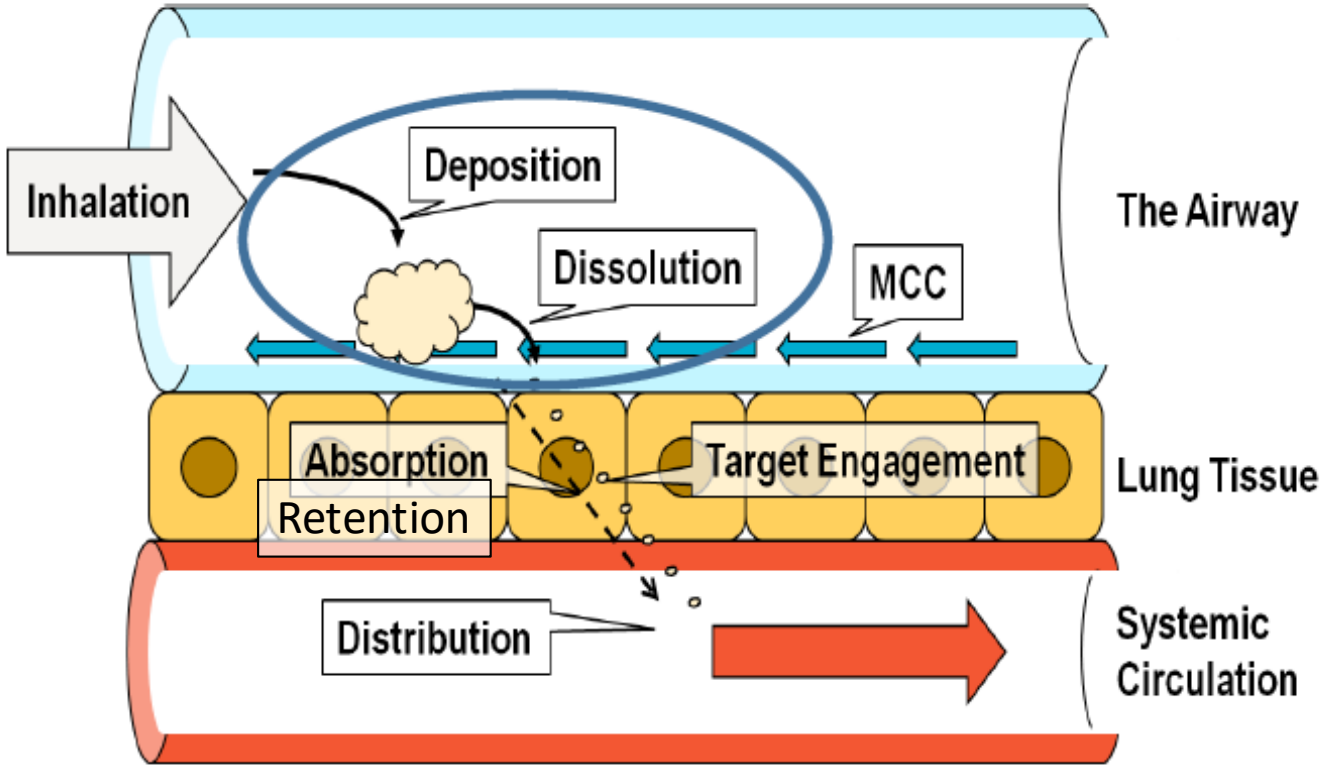
- **High Clearance**
- **Low Oral bioavailability**

Protein Binding





What "Events" are of Relevance for Pulmonary Fate ?



Modified from Olsson and Bäckman, Respiratory Drug delivery 2014

Deposition (dose + regional deposition)

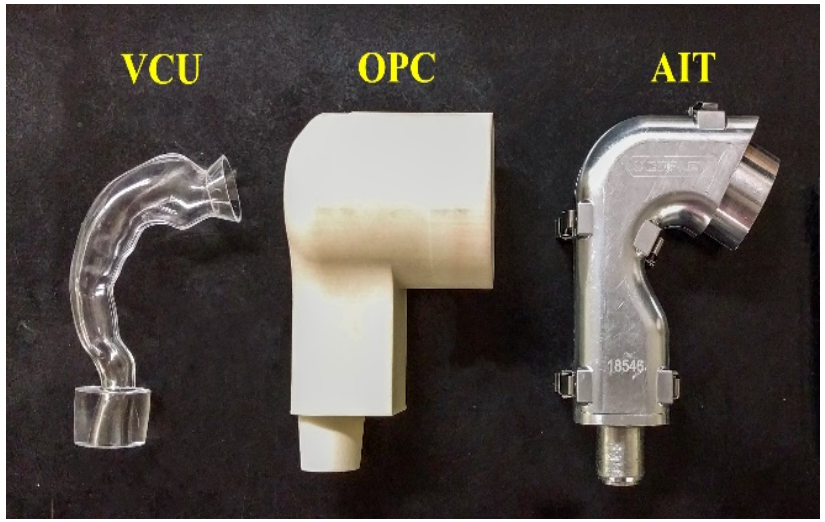
↓

Dissolution

↓

Permeation (Retainment)

Lung Dose: in vitro



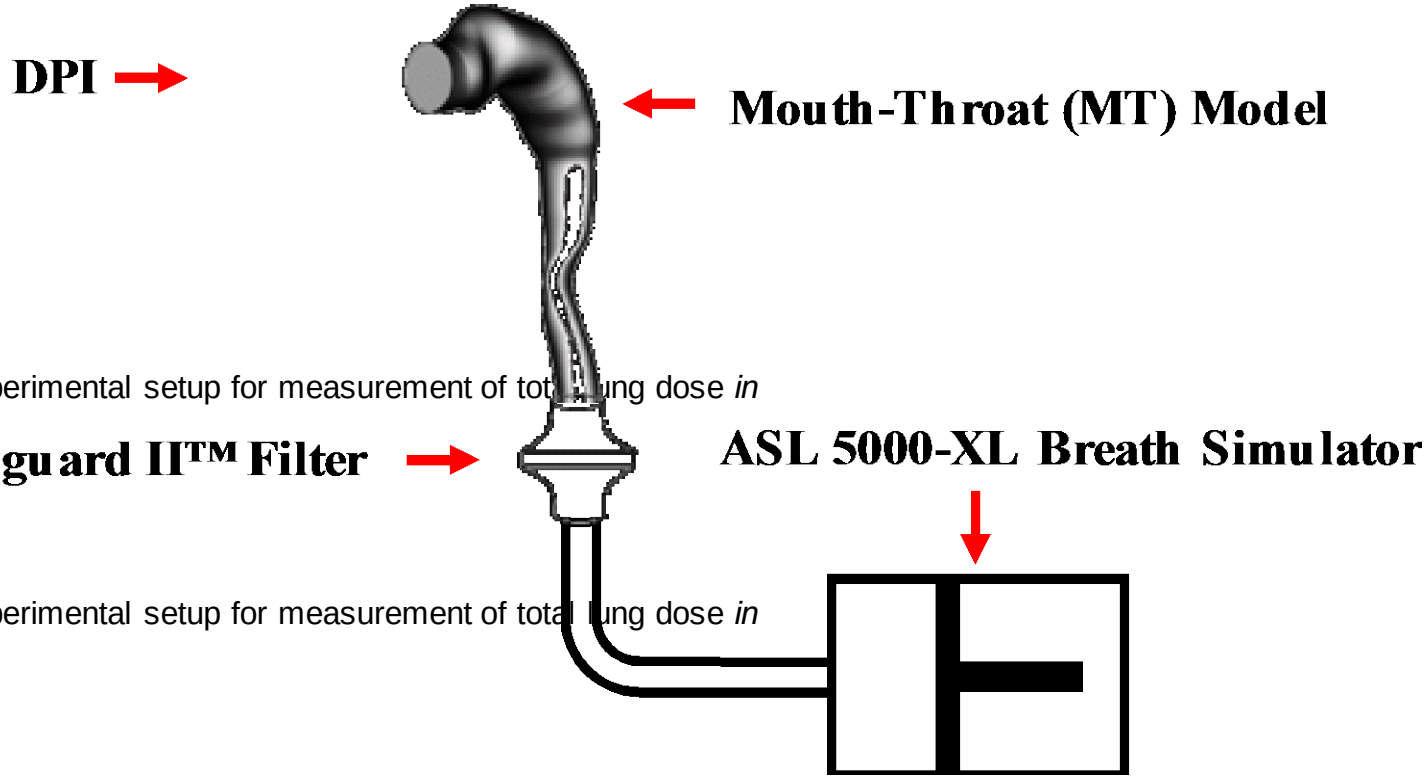


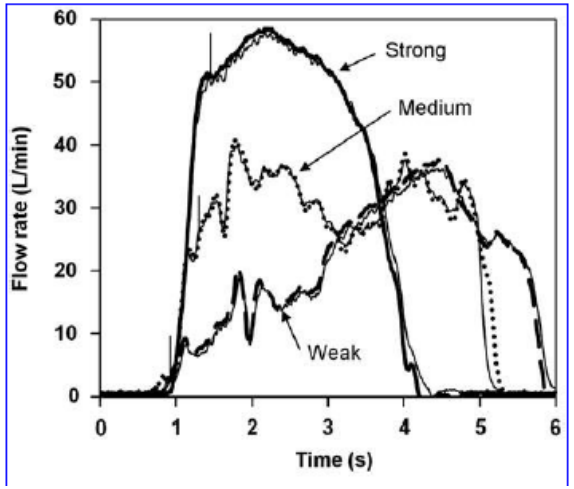
Figure 1. Schematic of experimental setup for measurement of tot[illegible]ung dose *in*

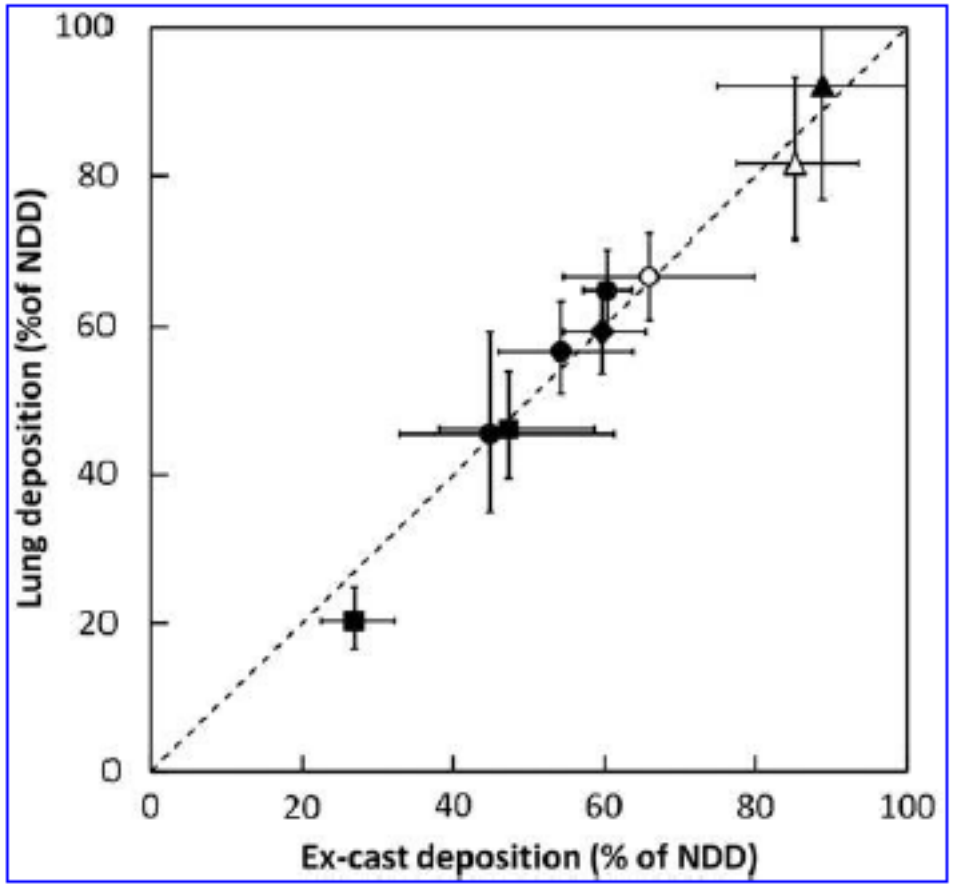
Figure 1. Schematic of experimental setup for measurement of total lung dose *in*

Lung deposition: in vitro/in vivo

Anatomical throat
Typical breathing pattern

ex-throat dose (filter or NGI)

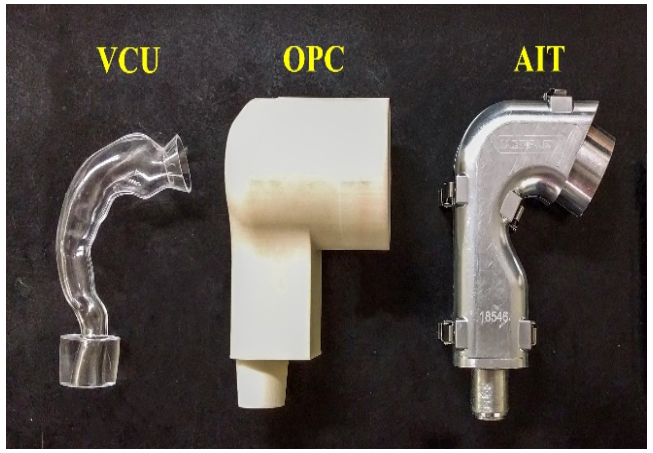


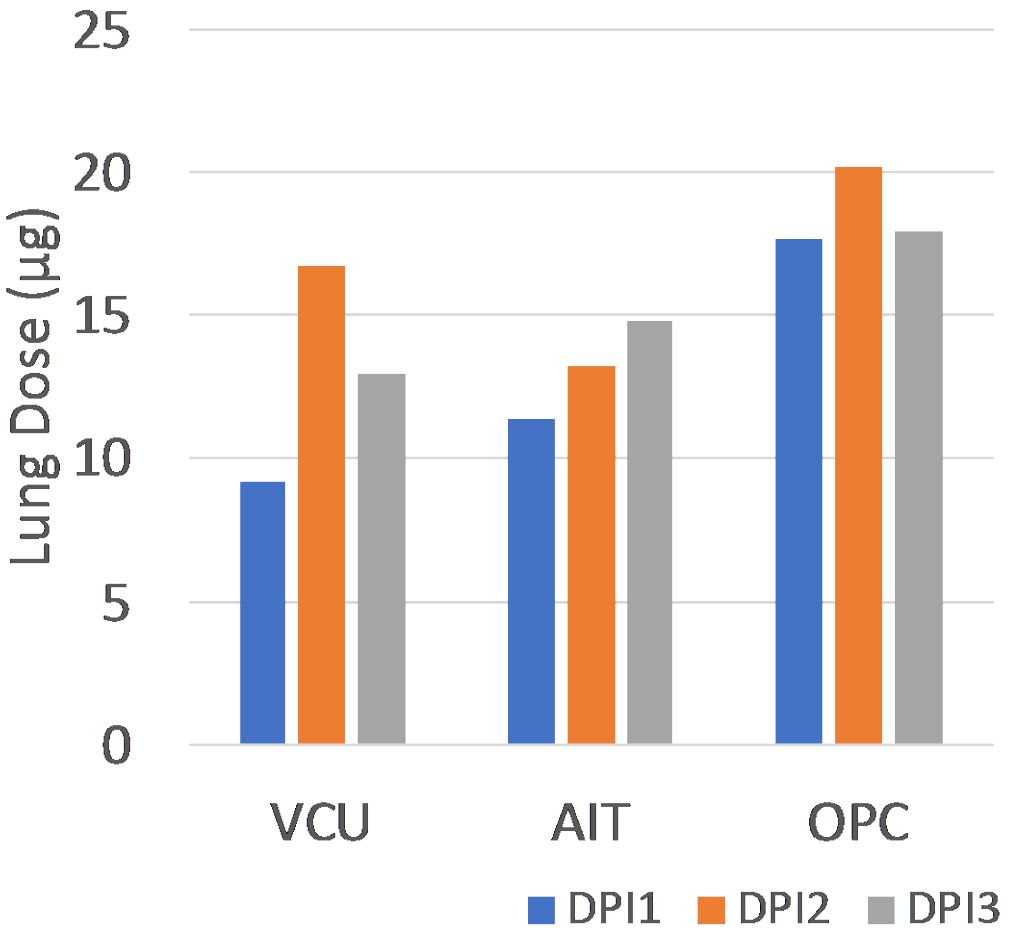


Bo Olsson et al. 2013

Further validation necessary

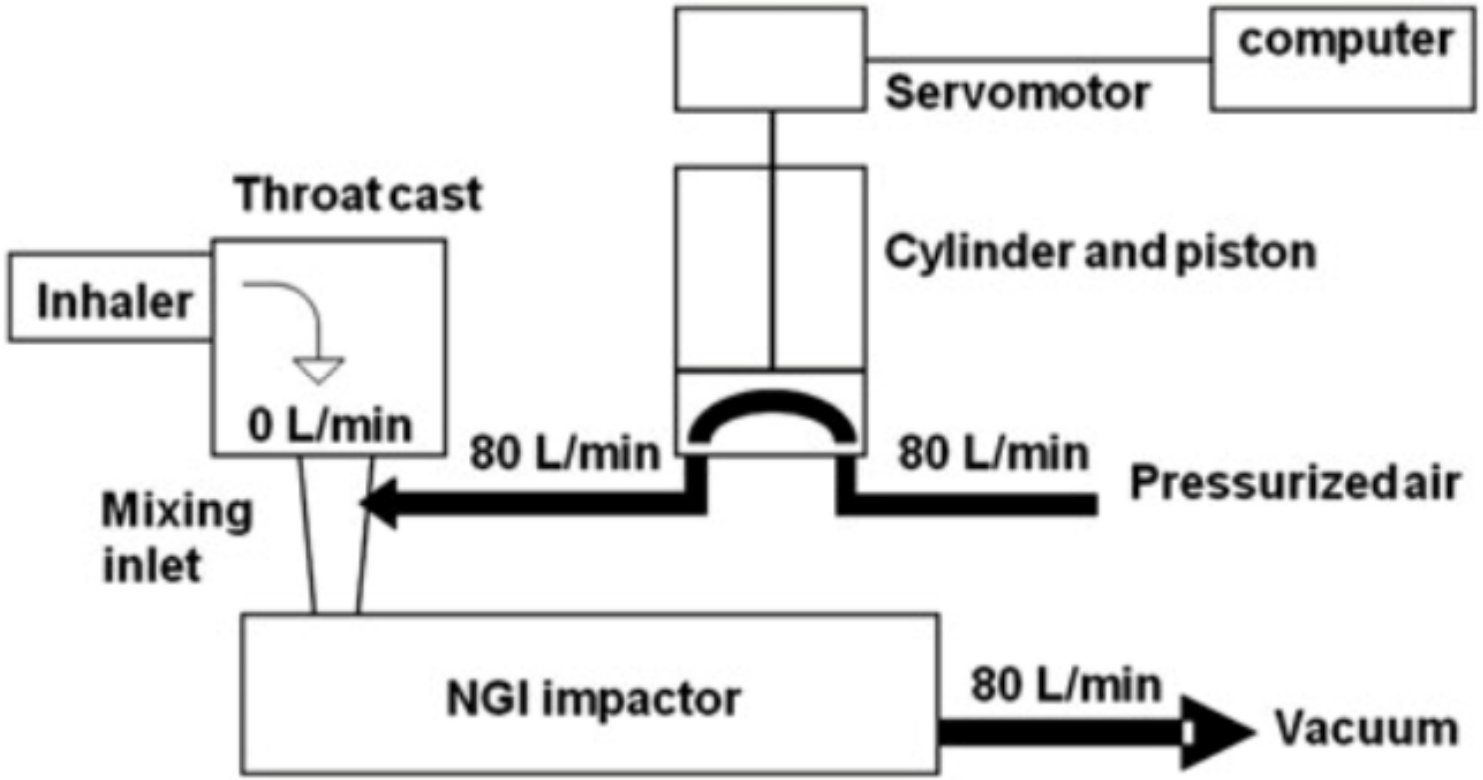
Comparison of 3 Throats





Throats differ!

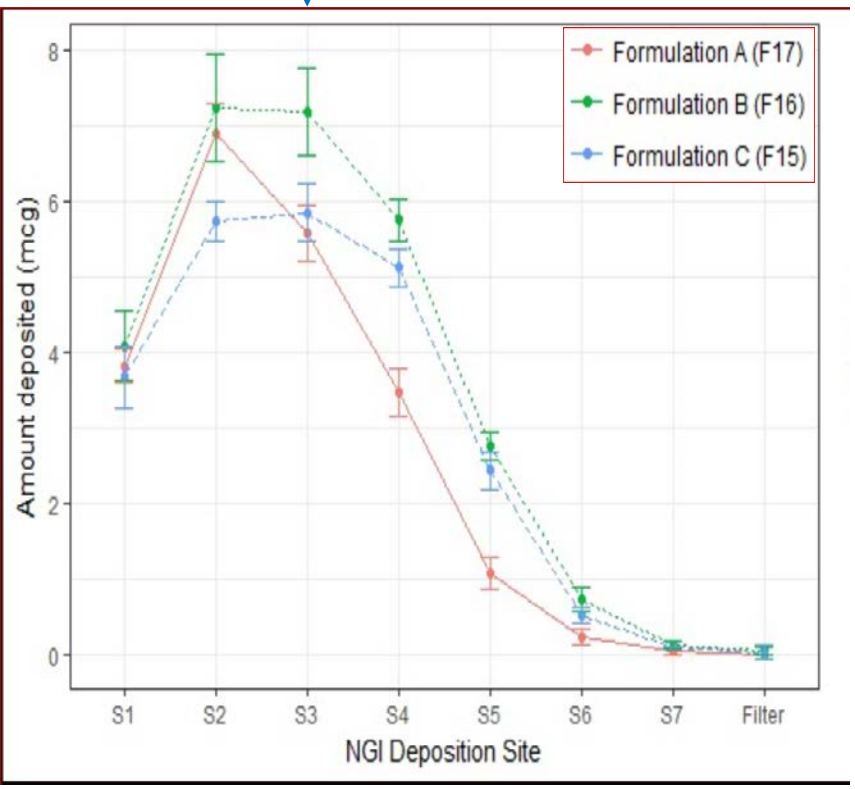
Regional Deposition: Cascade Impactor with Inhalation Flow



Bo Olsson et al. 2013

Regional deposition

Patient Inhalation Profile

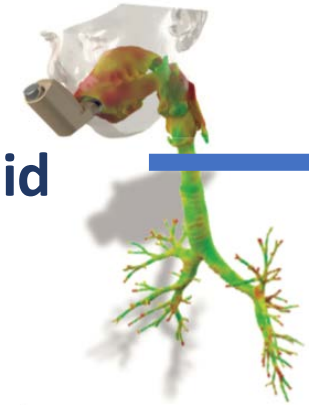


APSD

Algebraic Deposition Model
(NCRP66,NCRP66/ICRP 1994
Mimetikus Preludium

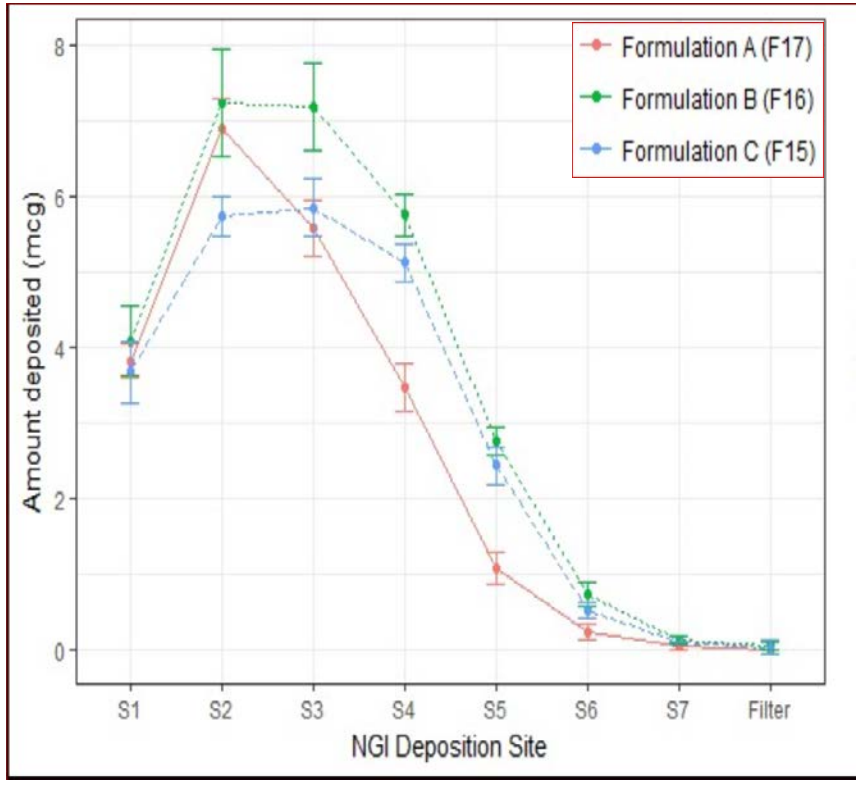
Regional deposition
Lung dose

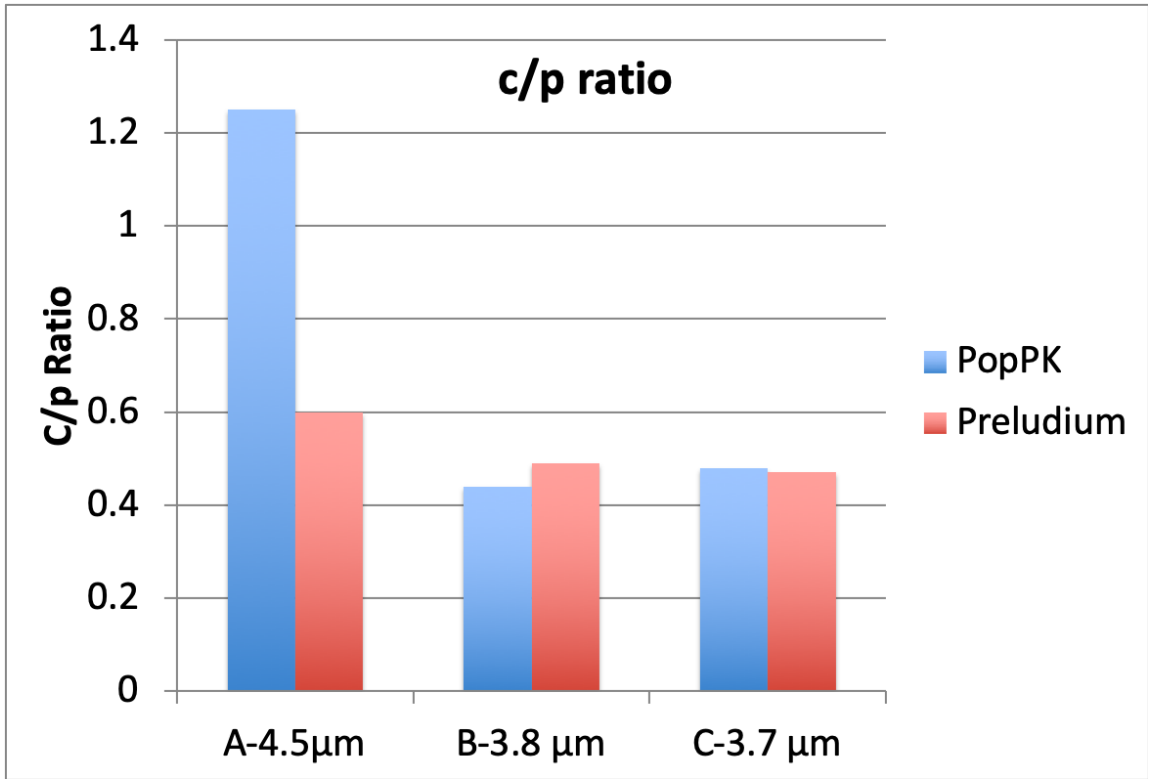
Computational Fluid Dynamics



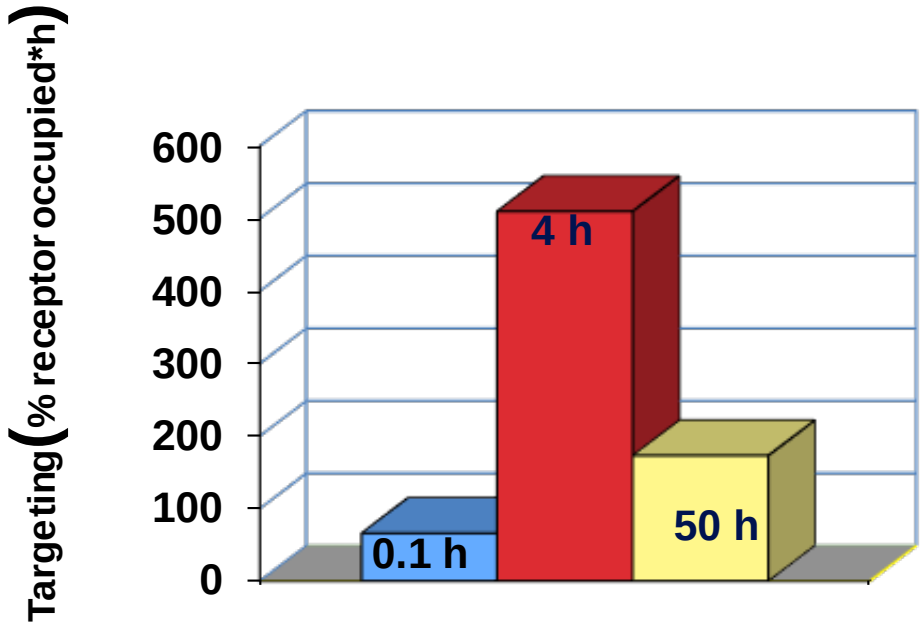
Regional deposition
Lung dose

Comparison: PK vs Algebraic Deposition Model





Dissolution rate, Mucociliary Transport and Pulmonary Selectivity



- There is an optimal dissolution rate, around mucociliary clearance rate
- If drug is soluble and reaches receptor, the lower permeability (lung/blood) the better

Method: Dissolution Tests

Sample Preparation

- DUSA >>> full range of particles
- Cascade Impactor >>> defined stage(s)
- Anatomical Throat >>> **ex-throat dose**

Dissolution Test Systems

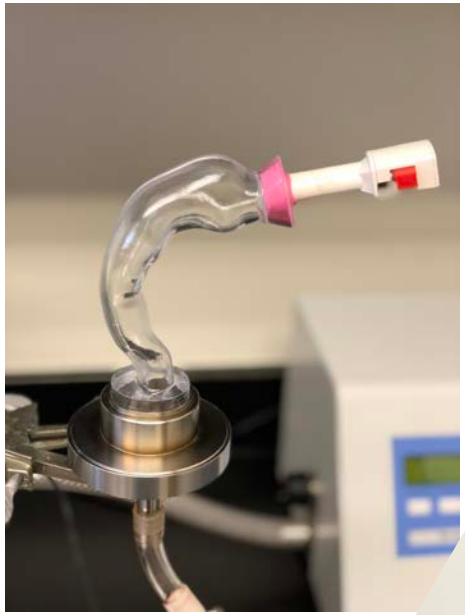
Systems Including diffusion across membrane (biomimetic)

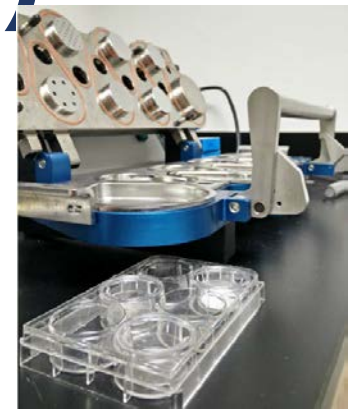
- Transwell system/Franz cell
- Dissolve it® system (Gerde et al., ASSAY and Drug Develop. Technol., 2017)

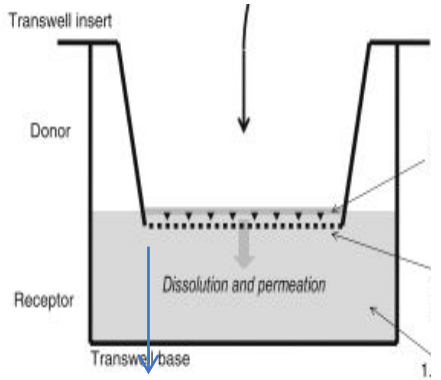
Systems without controlled membrane diffusion step

- USP II and IV

Applying the Dose (Inhalation)



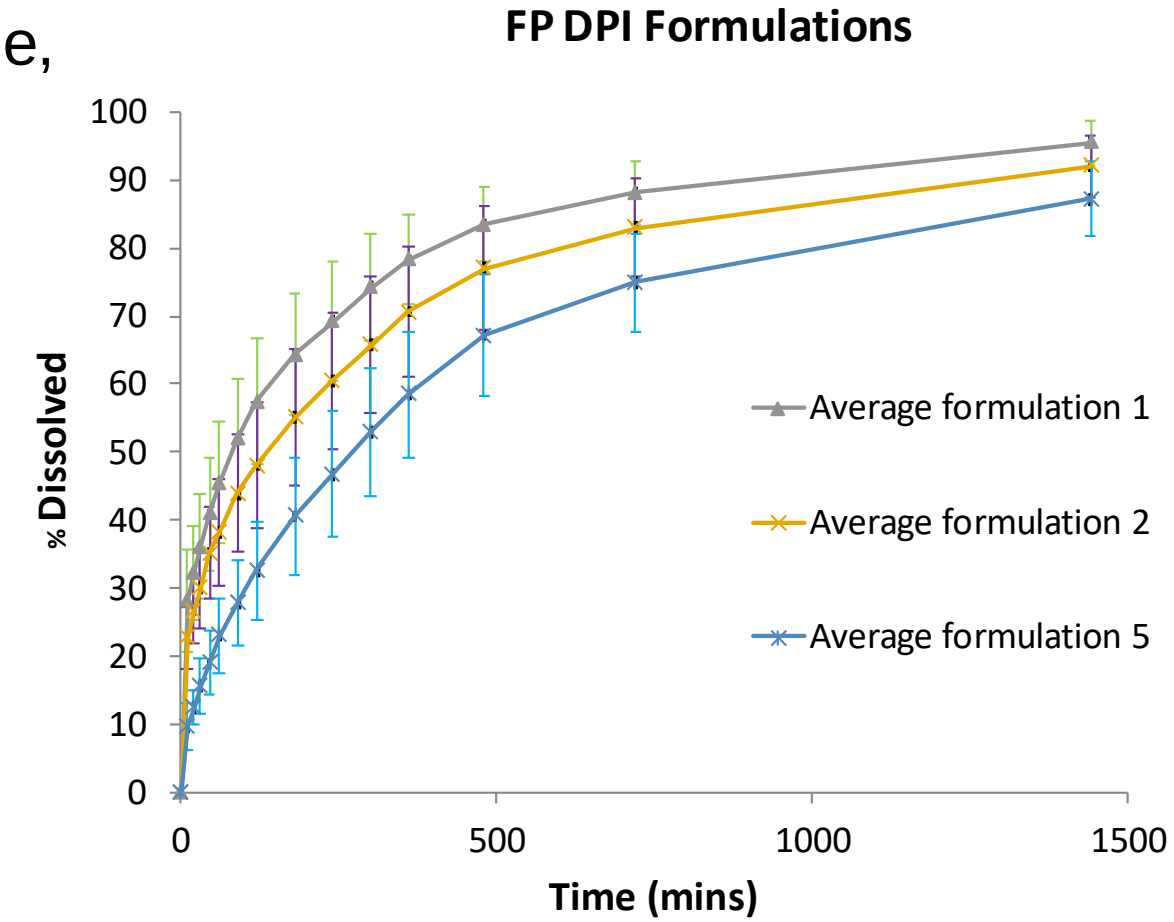




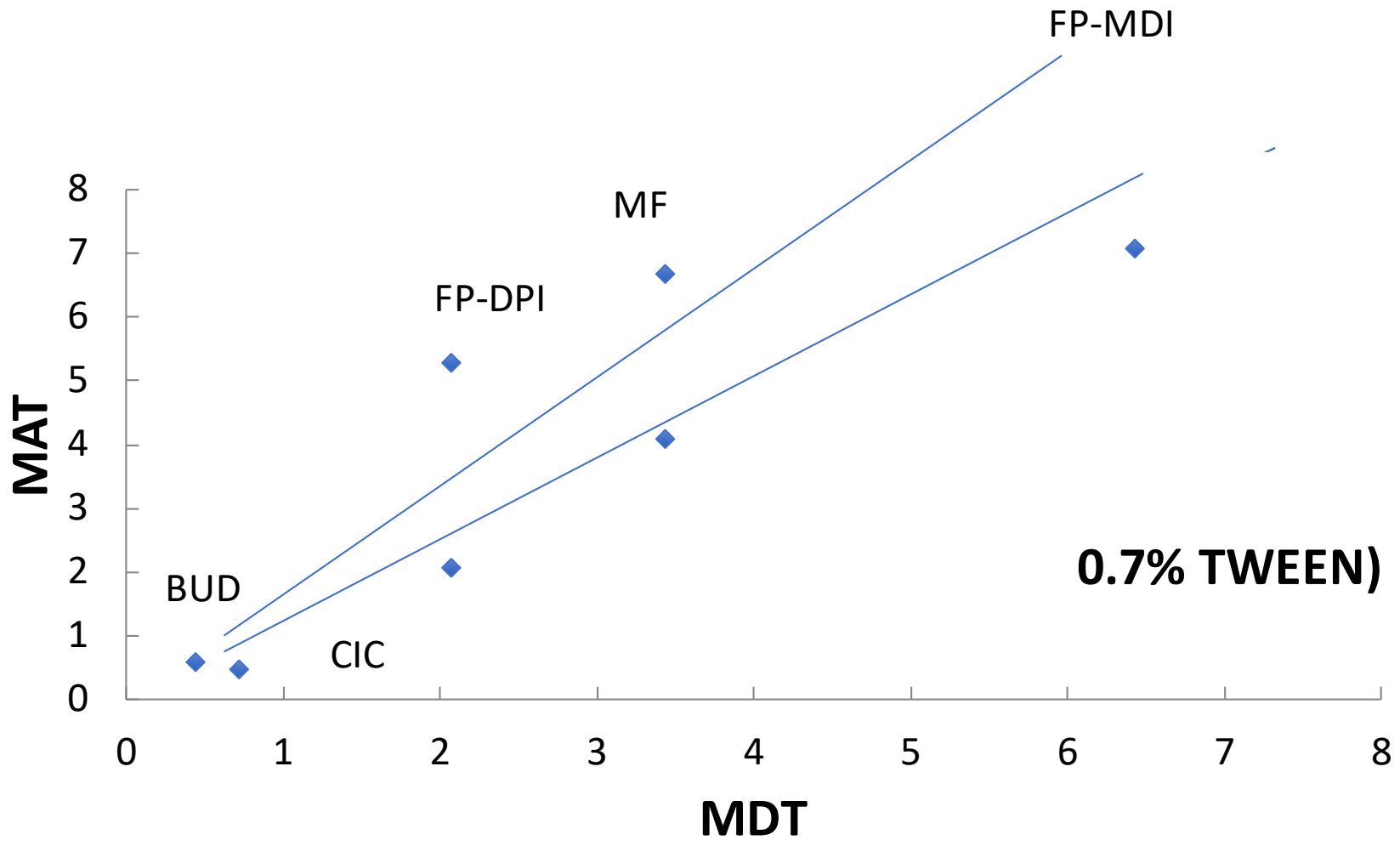
Arora, D., (2010)

Example: DPIs differing in lactose fines

- Fluticasone propionate (formulated UoB)
  - Same API, same API particle size,
  - different lactose fines

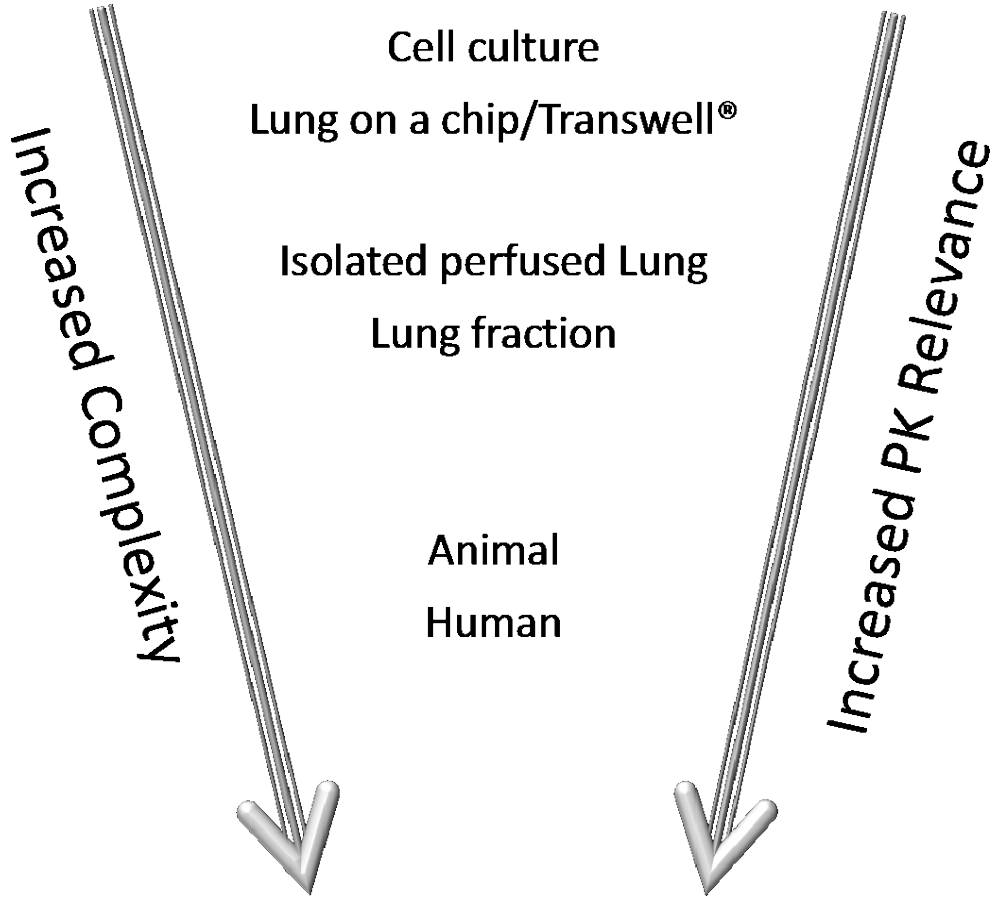


Correlation between MDT and MAT

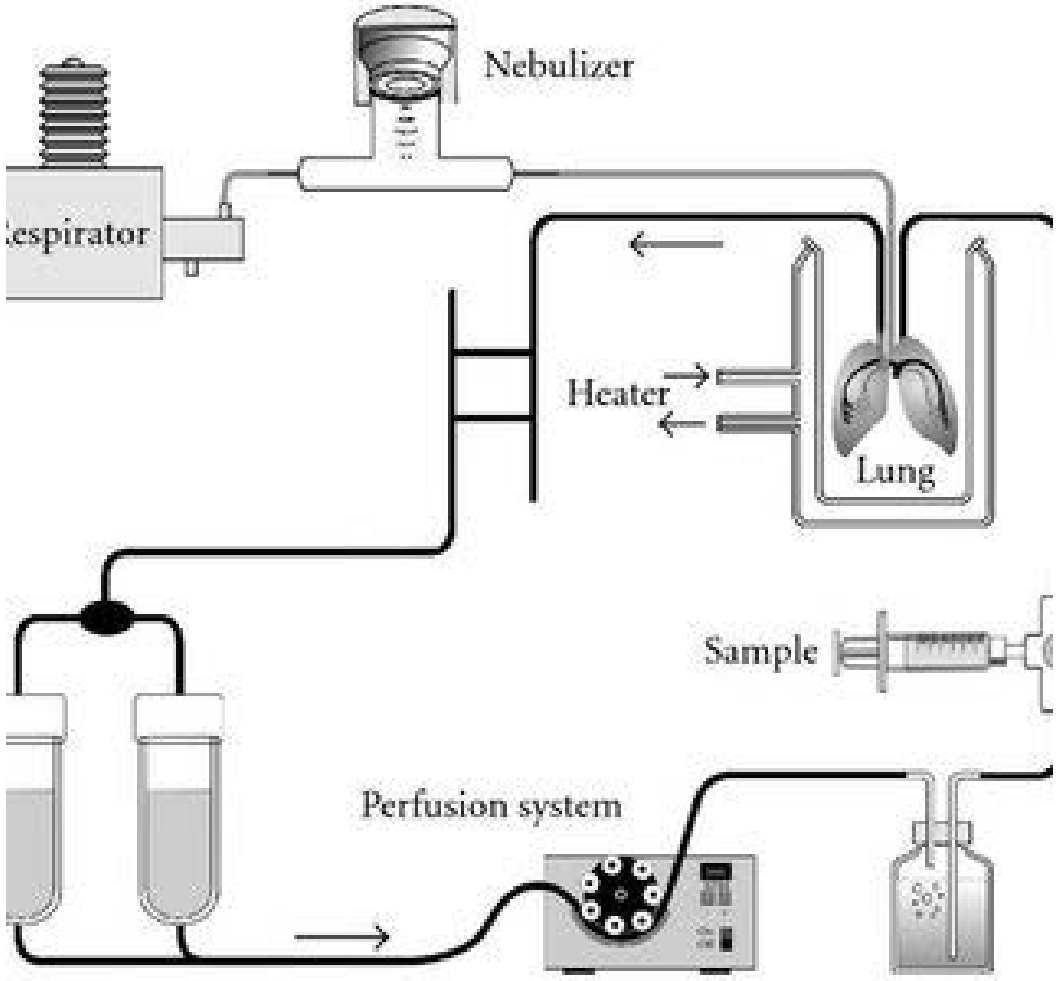


Correlation between MDT and MAT seems to exist

Methods to Assess Pulmonary Pharmacokinetics

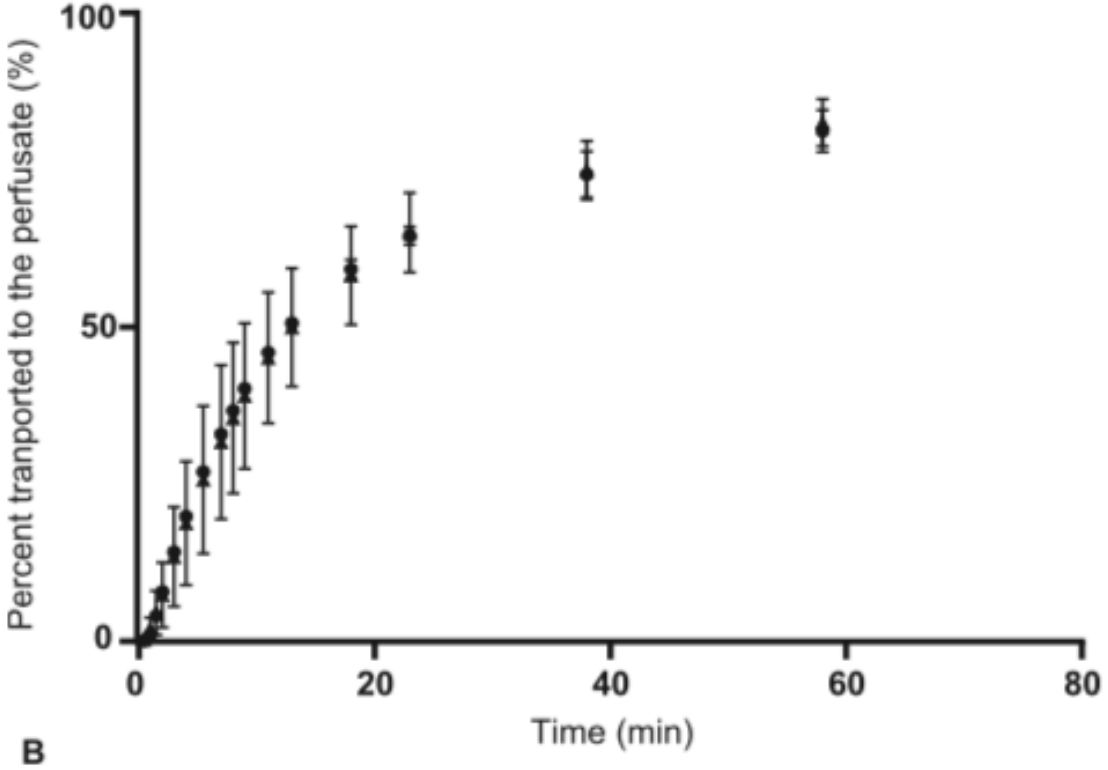


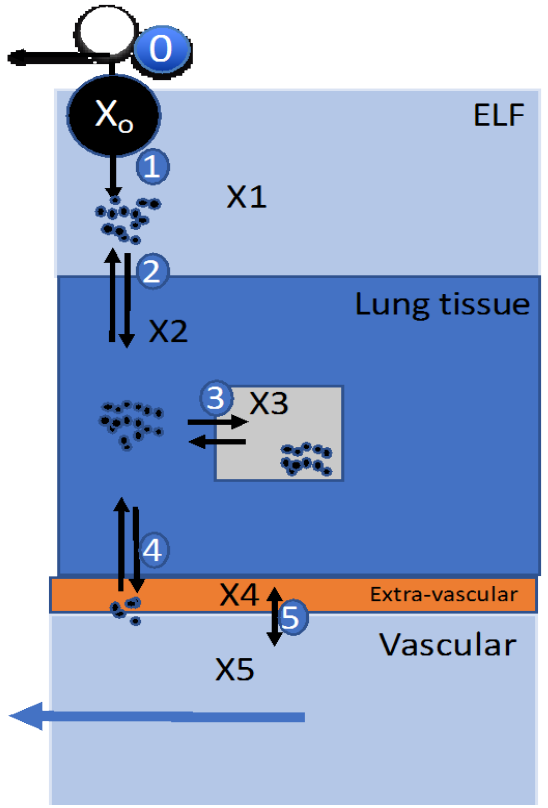
Isolated Perfused Lung



Pulmonary absorption – estimation of effective pulmonary permeability and tissue retention of ten drugs using an *ex vivo* rat model and computational analysis

Johanna Eriksson[a], Erik Sjögren[a], Helena Thörn[b], Katarina Rubin[c], Per Bäckman[b,1], Hans Lennernäs[a,*]





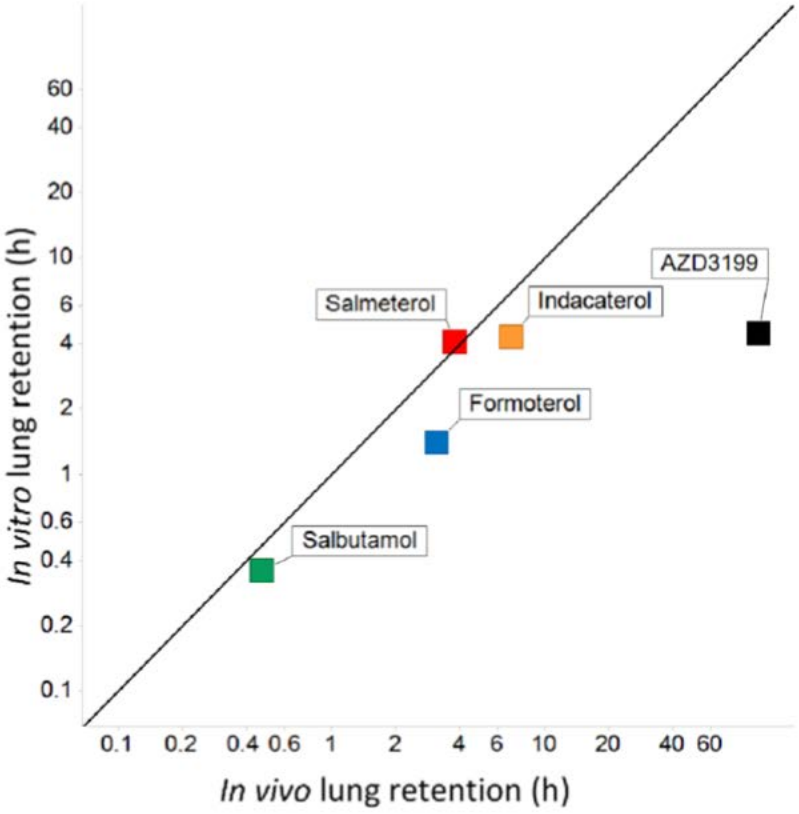
IPL is able to quantify fate of inhaled drug with relatively high resolution

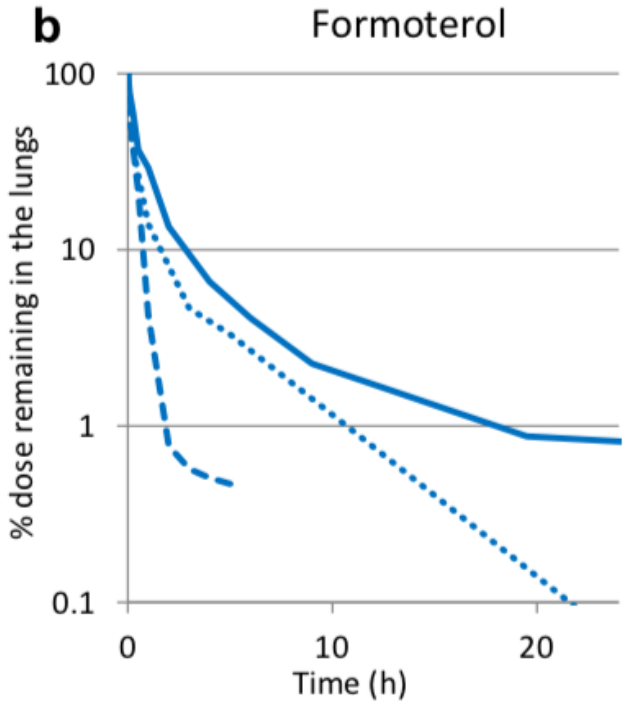
Pharmacokinetics, Pharmacodynamics and Drug Transport and Metabolism

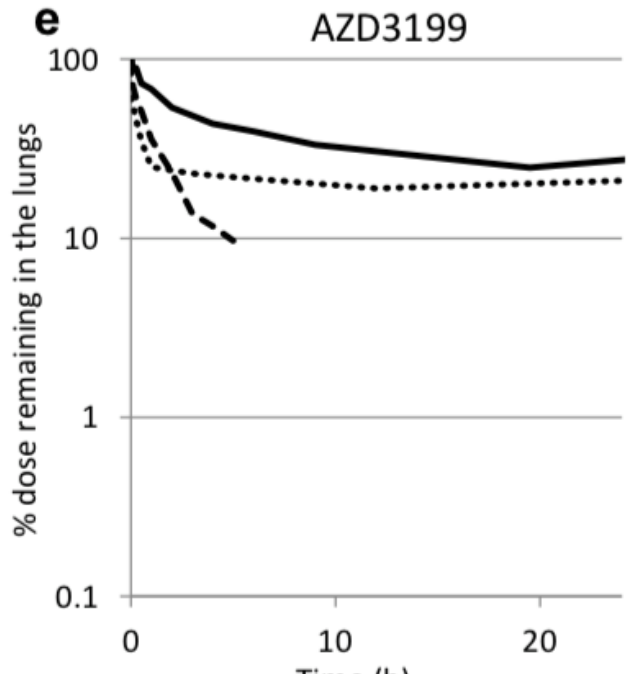
Lung Retention by Lysosomal Trapping of Inhaled Drugs Can Be Predicted *In Vitro* With Lung Slices

Erica Bäckström [1, 2, *], Elin Boger [2, 3], Anders Lundqvist [2], Margareta Hammarlund-Udenaes [1], Markus Fridén [1, 2]

[1] *Translational PKPD Group, Department of Pharmaceutical Biosciences, Uppsala University, Uppsala 751 24, Sweden*
[2] *Respiratory, Inflammation and Autoimmunity Innovative Medicines, AstraZeneca R&D Gothenburg, Mölndal 431 83, Sweden*
[3] *School of Engineering, University of Warwick, Coventry CV4 7AL, United Kingdom*







Permeability/Cell Culture Models of the Air-Blood Barrier

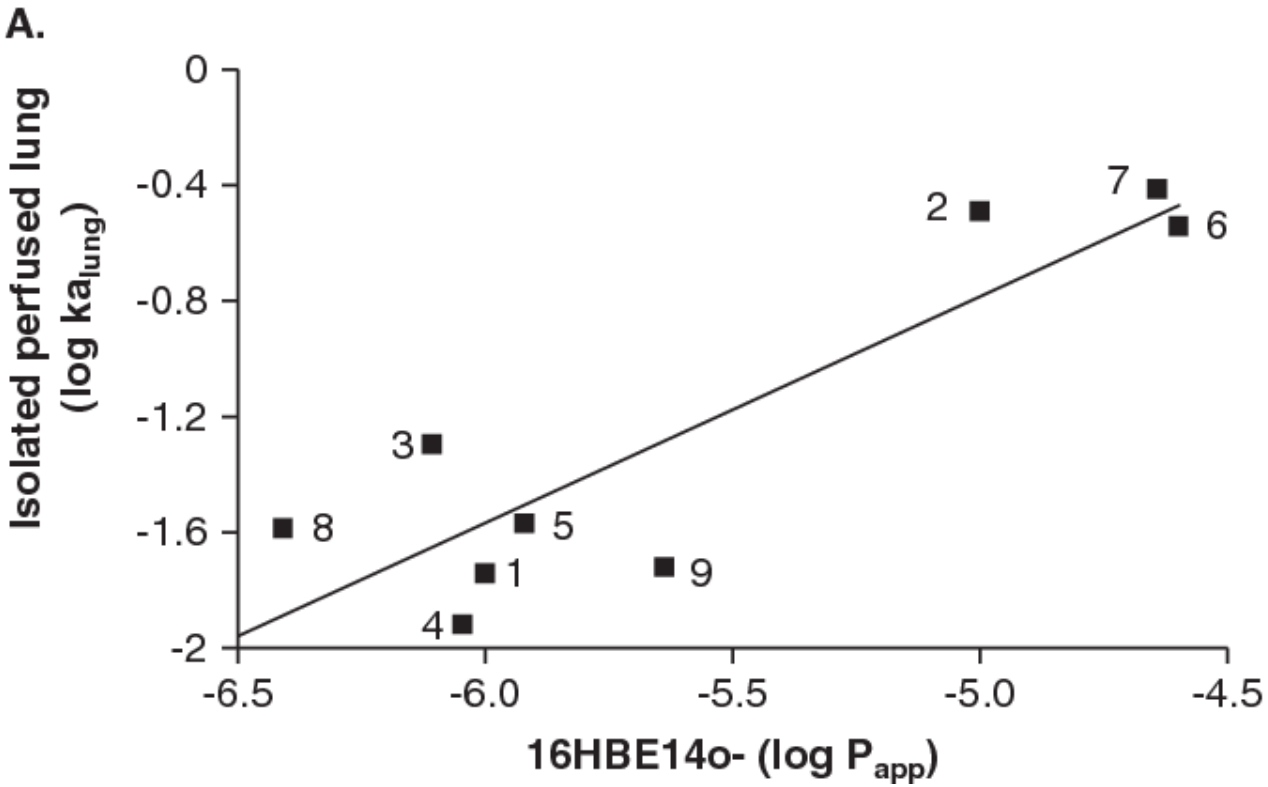
- **Cancer-derived cell lines:** Calu-3, A549, NCI-H441, and NCI- H292

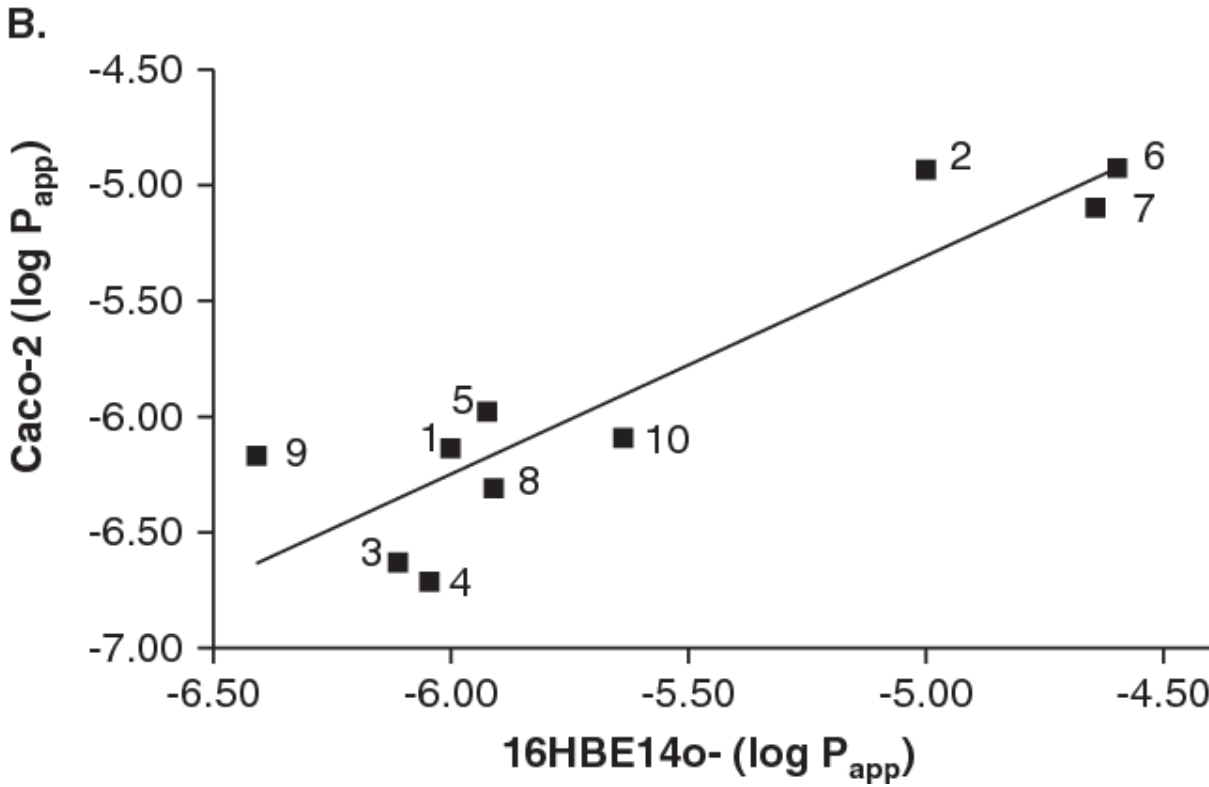
- **Simian virus (SV)40 large T antigen-immortalized cell lines**
  - 16HBE14o-
  - BEAS-2B

  often present phenotypes different from the original cell type.

- **Immortalized cell lines**:
  - NuLi-1, UNCN1T-3T, VA10, BCi-NS1.1, hAELVi

  close to native cells.





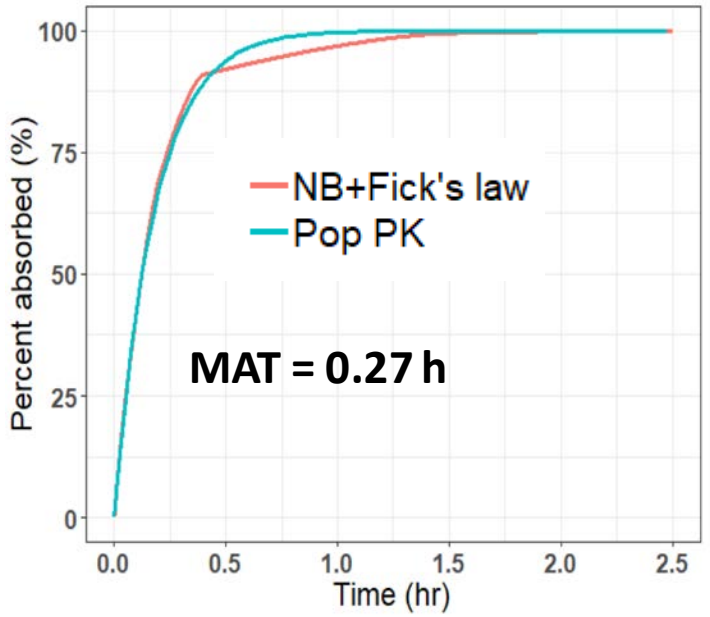
Published in Expert opinion on drug delivery 2009

Preclinical models for pulmonary drug delivery. Cláudia A Fernandes, Rita Vanbever

Combination of Dissolution/Permeability

Peripheral

Formulation C



Surface area: 60.2 *10^4 cm^2

Permeability Peff: 13.8*10^-3 cm/h (Eriksson)

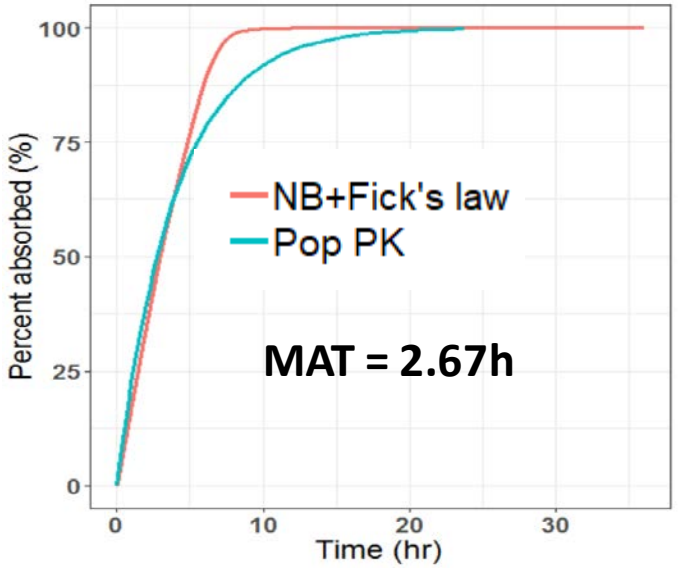
Relative Thickness of "airway": 1

Fitted Parameter:

Solubility: 0.73 µg/ml (Literature =0.5-1.4 µg/ml)

Central

Formulation C



Surface area: 1.00E+04 cm^2

Solubility: 0.73 µg/ml

Relative Thickness of "central airway": **24**

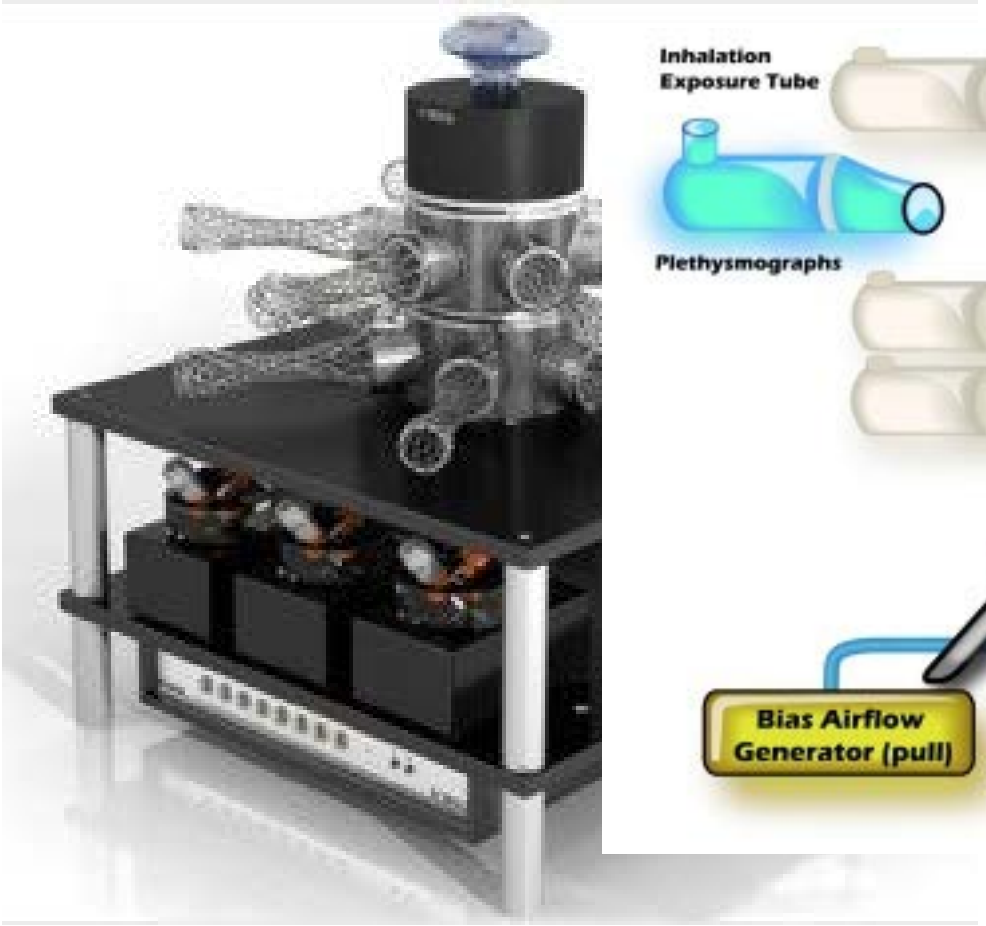
Fitted Parameter:

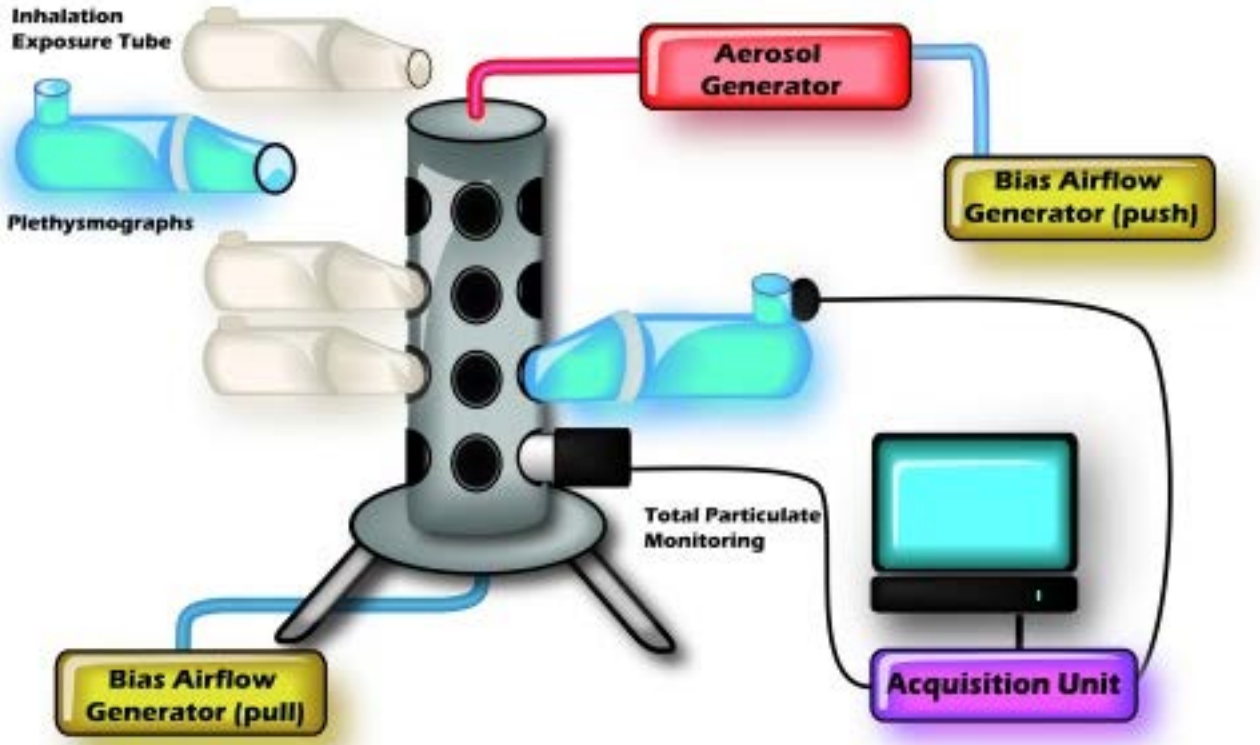
Permeability: 0.7*10^-3 cm/h

Relative permeability: `13.8/0.7= 20

Guinea Pig	• **Easily sensitized and challenged** • **Good model for airway disease** • **Immediate and late phase response** • **Model for COPD (cigarette smoke)**
Rat	• Low cost • Easily sensitized and challenged (**Sephadex**) • Model for COPD (cigarette smoke)
Mice	• Low cost • Easily sensitized and challenged • Transgenic technology • Model for COPD (cigarette smoke)
Cat	• Distal Lung Anatomy and • Idiopathic bronchial disease similar to humans
Dog	• Sensitive to allergens, shows atopy • Eosinophils are present • Long term change in pulmonary function
Equine	• Heaves-airway disease with some hallmarks of human asthma.
Sheep	• Sensitive to allergens • Immediate response to inhaled allergens • Shows Airway Hyper Responsiveness

MV Aun et al "Animal Models of Asthma: Utility and Limitations." Journal of Asthma and Allergy 10 (2017): 293–301

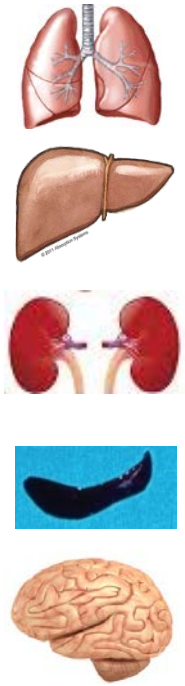



Inhalation
Exposure Tube
Plethysmographs
Aerosol
Generator
Bias Airflow
Generator (push)
Total Particulate
Monitoring
Bias Airflow
Generator (pull)
Acquisition Unit

Ex-vivo Receptor Binding Studies

Intravenous injection (IV)
Intratracheal instillation (IT)
(n=3-6 per timepoint)

100 µg/kg
BDP
BMP
BUD
CIC
Des-CIC
FP
TA

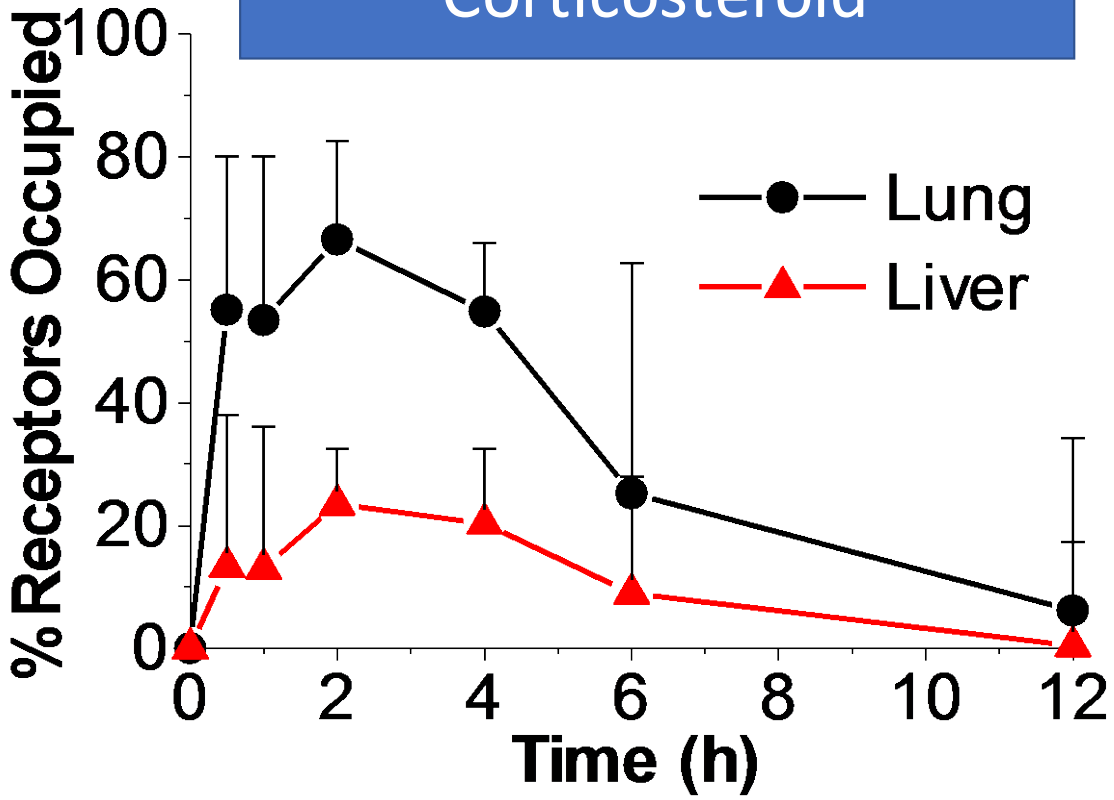


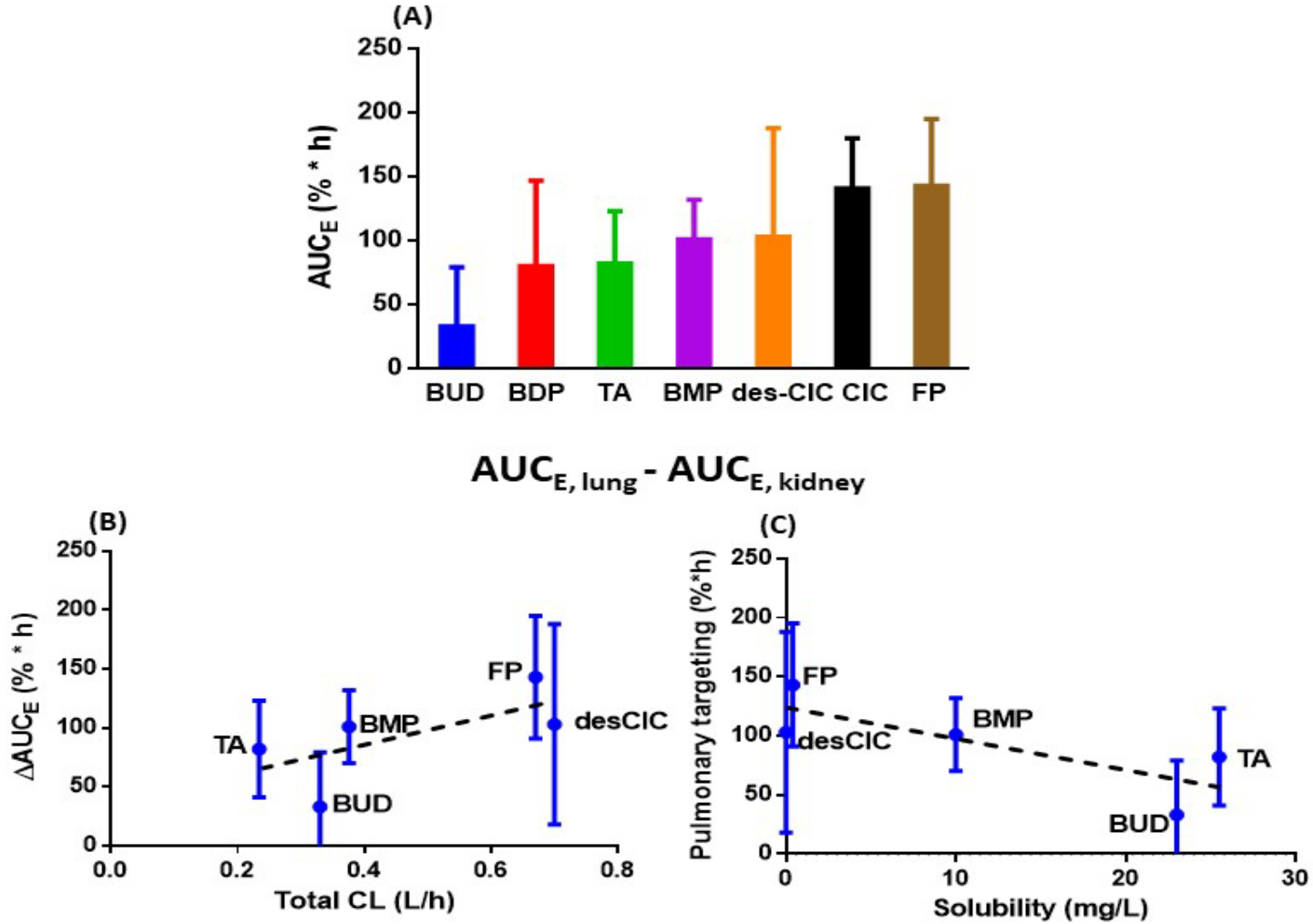
Specific binding
Tracer: ^{3}H-TA

$$\text{Free receptors (\%)} = \frac{Specific\ binding\ in\ trt\ group}{Spcific\ binding\ in\ ctr\ group}$$

Pulmonary Targeting
In Rat Ex-vivo Receptor Binding Assay

Intratracheal
Corticosteroid




(A)
250
200
150
100
50
0
AUC_E (% * h)
BUD
BDP
TA
BMP
des-CIC
CIC
FP
AUC_E, lung - AUC_E, kidney
(B)
ΔAUC_E (% * h)
TA
BMP
FP
desCIC
BUD
0.0
0.2
0.4
0.6
0.8
Total CL (L/h)
(C)
Pulmonary targeting (%*h)
FP
desCIC
BMP
TA
BUD
0
10
20
30
Solubility (mg/L)

Summary

- Array of preclinical methods is available to evaluate NCI for inhalation therapy
- Further improvements necessary to predict *regional deposition* with higher resolution
- Further improvements necessary to identify *pulmonary retainment*

Acknowledgments

FDA Contracts and Grants (GDUFA)

- HHSF223201110117A,
- HHSF223201610099C,
- HHSF223201300479A
- 1U01FD004950

- M. Hindle's group (VCU)
- J. Bulitta (UF)
- Graduate students (S. Bhagwat, M. Cheng, J. Shao)

Questions

This slide will stay visible during your Q&A. You may add your contact information, a web address, or other information that participants would need to follow-up on your talk.

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