Leveraging Plasma and Urine Concentrations to Understand the Pulmonary Fate of Inhaled Drugs

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Notes

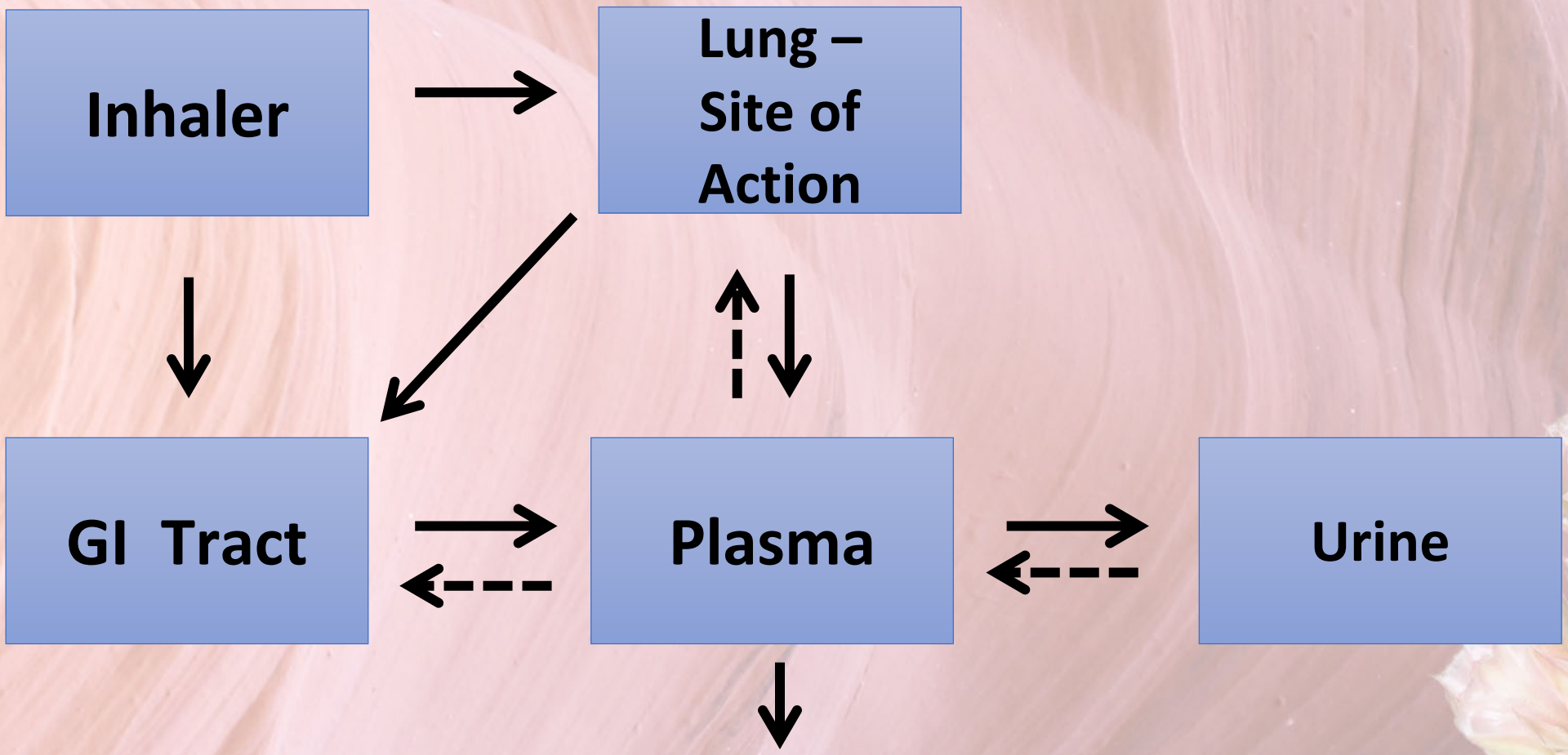
- Presented concepts are similarly applicable to other local drug administration routes (e.g., intravitreal)
- However, adjustment taking target organ anatomy and physiology into account may be required

Unglamorous

Highly Impactful

- **Determine pulmonary residence time of inhaled drugs**
- **Confirm existing and generate new hypothesis of pulmonary fate of inhaled drugs**
- **Key component for streamlining and accelerating the pre-clinical and clinical development of new drugs**

What is the Challenge?



Method: Deconvolution by Parametric Convolution

IV Data	Inhalation With Charcoal	Inhalation
Healthy Subjects	Healthy Subjects	Healthy Subjects & Patients

Bartels, C., Looby, M., Sechaud, R. and Kaiser, G. (2013), Pharmacokinetics of glycopyrronium in the lung. Br J Clin Pharmacol, 76: 868-879. https://doi.org/10.1111/bcp.12118

Key Assumptions

Route of Administration

Disease Population

Inhaled Glycopyrronium – Breezehaler® Powder & Healthy Subjects

Pulmonary Bioavailable Fraction 52.6%

Absorption Process	Absorption Half-Life (h)	Fraction Absorbed (%)
Slow	80	79
Intermediate	0.45	9
Fast	< 0.03	12

Authors did not propose a mechanistic explanation of the different lung absorption processes based on the available data

Bartels, C., Looby, M., Sechaud, R. and Kaiser, G. (2013), Pharmacokinetics of glycopyrronium in the lung. Br J Clin Pharmacol, 76: 868-879. https://doi.org/10.1111/bcp.12118

Inhaled Olodaterol – Respimat®
Solution & Healthy Subjects; Plasma and Urine Data

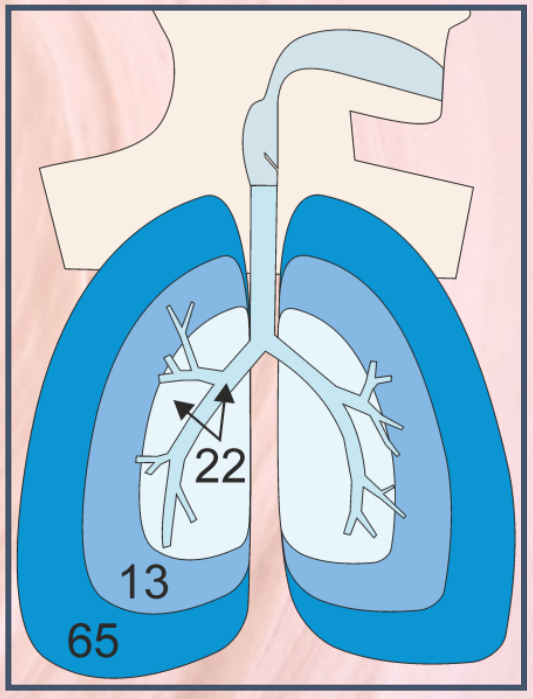
Pulmonary Bioavailable Fraction 49.4 %

Absorption Process	Absorption Half-Life (h)	Fraction Absorbed (%)
Slow	21.8	70.1
Intermediate	2.00	26.6
Fast	0.268	3.31

Pulmonary absorption half-lives of small molecules with log octanol–water partition coefficients like that of olodaterol (the log D value at pH 7.4 is 1.2 21) are generally assumed to be between 1 min and 1 h

Borghardt, J. M., Weber, B., Staab, A., Kunz, C., Formella, S., and Kloft, C. (2016) Investigating pulmonary and systemic pharmacokinetics of inhaled olodaterol in healthy volunteers using a population pharmacokinetic approach. *Br J Clin Pharmacol*, 81: 538– 552. doi: 10.1111/bcp.12780.

Inhaled Olodaterol – Respimat®
Solution & Healthy Subjects



% of the lung dose in different airway generations: Trachea-G14 (light blue), G15-20 (blue), G21-alveoli (dark blue)

PK Modelling Results	
Slow	70.1 %
Intermediate	26.6 %
Fast	3.31 %

Based on physico-chemical properties, lysosomal trapping may be potential explanation

Ciciliani A-M, Wachtel H, Langguth P. Respiratory Drug Delivery; 2014; Fajardo, Puerto Rico: Davis Healthcare International Publishing, LLC.

Inhaled Olodaterol – Respimat® Solution & Asthma/COPD Patients

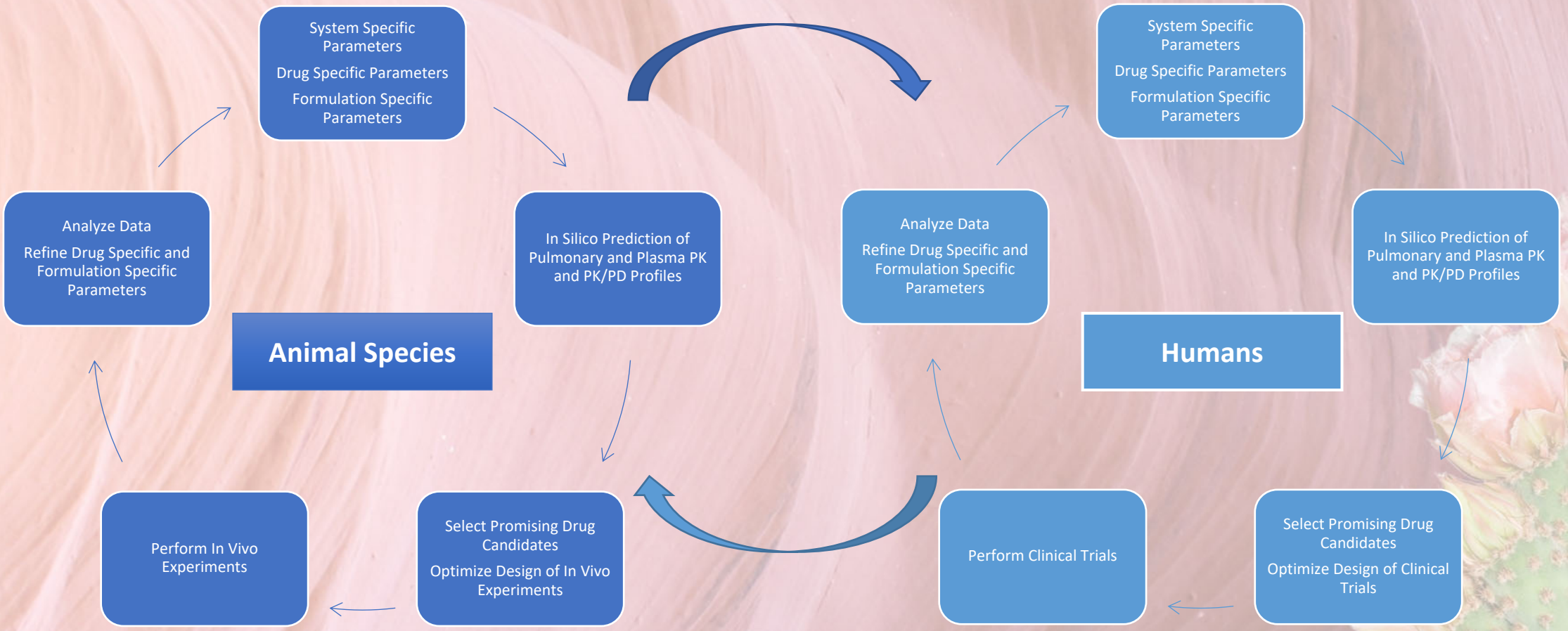
	Healthy	COPD	Asthma
Pulmonary Bioavailable Fraction (%)	48.7	53.6	48.7
	Fraction Absorbed (%) | Absorption Half-Life (h)		
Slow	74.6 | 18.5	80.1 | 37.8	87.2 | 18.5
Intermediate	21.6 | 1.55	16.9 | 1.55	10.9 | 1.55
Fast	8.81 | 17.3 min	2.98 | 9.7 min	1.92 | 9.08 min

Caucasian, non-smoker with BSA 1.89m^2

BSA, smoking status and race affect pulmonary PK parameters

Borghardt, J. M., Weber, B., Staab, A., Kunz, C., and Kloft, C. (2016) Model-based evaluation of pulmonary pharmacokinetics in asthmatic and COPD patients after oral olodaterol inhalation. Br J Clin Pharmacol, 82: 739– 753. doi: 10.1111/bcp.12999.

Translational Pharmacology



Key Messages

Plasma and urine data after inhalation can be leveraged to

- **Determine pulmonary residence time of inhaled drugs**
- **Confirm existing and generate new hypothesis of pulmonary fate of inhaled drugs**
- **Streamline and accelerate the pre-clinical and clinical development of new drugs**

Acknowledgements

- Jens Borghardt
- Guenther Hochhaus
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