ASSESSING THE IMPACT OF REALISTIC BREATHING PROFILES IN AEROSOL DEPOSITION USING IN-SILICO METHODS

Carolina Dantas [1], Ulf Krüger [1], William Ganley [2] Robert Bootle [2], Hosein Sadafi [3], Ana Costa [3], Janis Shute [4]*

[1] Pulmotree Medical GmbH, Munich 80333, Germany / [2] Nanopharm Ltd an Aptar Pharma Company, Cwmbran NP44 3WY, UK / [3] Fluidda, Groeningenlei 132, 2550 Kontich Belgium / [4] Ockham Biotech Ltd, Hampshire PO16 0BH, UK

* In memory of Professor Janis Shute

DDL2024 DRUG DELIVERY TO THE LUNGS

Introduction:

This study addresses the challenges of aerosol delivery of biologics to targeted lung regions, emphasizing the role of the breathing manoeuvre. Traditional in-vitro testing is based in standardized unrealistic breathing profiles, causing discrepancies with real patient use.

The Kolibri™ Mesh Nebuliser (PULMOTREE, figure 1) incorporates a feedback technology to guide inhalation and capture real-time data about the patient´s breathing manoeuvre [1-3], enabling the use of realistic breathing profiles for aerosol delivery testing.

Goal: to assess the regional lung deposition of nebulised OCK4 with two in-silico methods, RDM and FRI, to compare:

Spontaneous unguided breathing profile **VS** Realistic Kolibri™ guided breathing profile

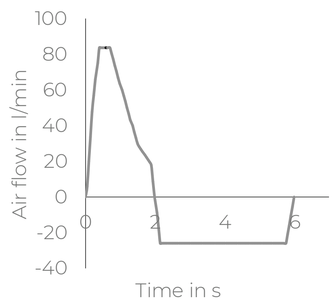
Methods:

OCK4 (Ockham Biotech Ltd) is a biologic developed to target the small airways and alveoli. Aerosol characterisation with the Kolibri™: MMAD 3.26 µm, Delivered Dose 58.1 mg.

The breathing profiles description:

Spontaneous Unguided Breathing Profile [4]

- 1500mL inhaled volume
- peak inspiratory flow 80L/min
- I:E ratio 1:2
- Respiratory Rate = 10 cpm



VS

Realistic Kolibri™ Guided Breathing Profile [3]

Based on real users' data

- 1500mL inhaled volume
- peak inspiratory flow 15L/min
- I:E ratio 1,6:1
- Respiratory Rate = 6 cpm

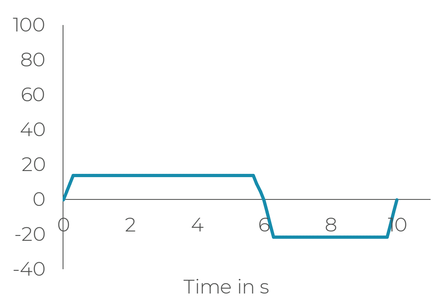


Figure 1 – The Kolibri ™ Mesh Nebuliser (PULMOTREE)

Results and Discussion:

1. Regional Deposition Modelling (RDM) in a healthy lung

The RDM is based on the NCRP model implemented in the Mimetikos Preludium™ software and configured for the Weibel model of the lung. The RDM predicted the regional lung deposition of OCK4 comparing the two breathing profiles in a healthy lung model – illustrated in Figure 2.

The realistic Kolibri ™ guided breathing profile had:

- 45% higher deposition in the OCK4 target regions (bronchiolar + alveolar) compared to the spontaneous breathing profile
- a more favourable pattern for deep lung deposition due to higher AI deposition (41.3% vs 27.9%) and lower ET deposition (12.4% vs 23.4%)

Spontaneous unguided breathing profile **VS** Realistic Kolibri™ guided breathing profile

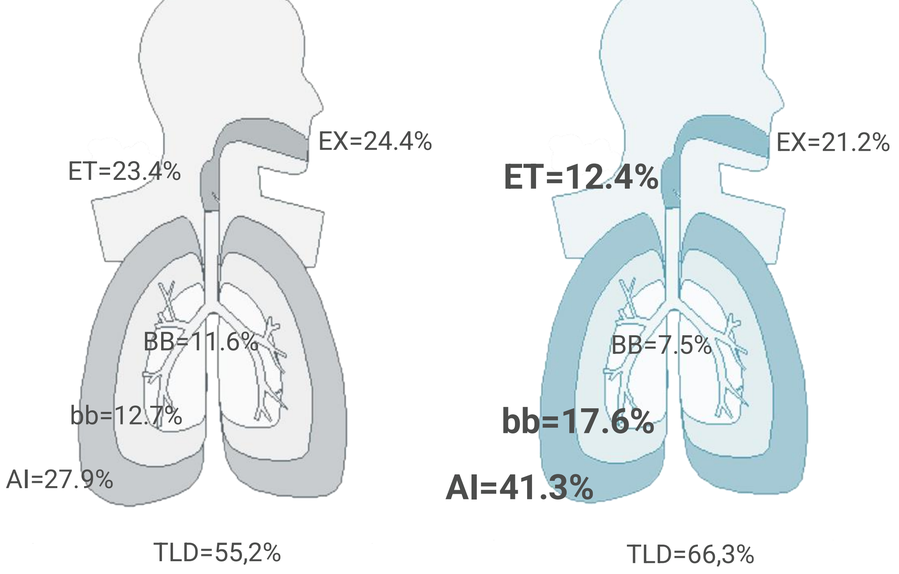


Figure 2 – RDM predicted lung deposition (mean % of DD) in the extra thoracic (ET), tracheobronchial (BB; generations 1-8), bronchiolar (bb; generations 9-15), alveolar-interstitial (AI; generations 16-23) regions and the exhaled fraction (EX). Total Lung Deposition (TLD; sum of BB+bb+AI).

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2. Functional Residual Imaging (FRI) in diseased models

FRI is based on 3D respiratory tract models from CT scans, in which computational fluid dynamics to simulate flow and particle behaviour. FRI estimated the regional lung deposition of OCK4 with the Kolibri comparing the two breathing profiles in a patient with Cystic Fibrosis (CF) (figure 3) and a patient with non-CF bronchiectasis (NCFB). The results are described in Table 1.

Compared to the spontaneous profile, the realistic Kolibri™ guided breathing profile had:

- Lower extra-thoracic and higher intrathoracic deposition in both CF and NCFB patients
- Higher peripheral deposition: 58.8% (CF) and 51.4% (NCFB)

In both disease models, the results are favourable for respiratory drug delivery and reveal a similar regional deposition.

Table 1 – FRI predicted lung deposition (% of DD) of nebulised OCK4 comparing two different breathing profiles in a CF and NCFB patient

	Spontaneous unguided Breathing Profile		Realistic Kolibri™ Guided Breathing Profile	
	CF Patient	**NCFB Patient**	**CF Patient**	**NCFB Patient**
Extra Thoracic (%)	25.21	24.24	**16.52**	**19.06**
Intrathoracic (%)	58.07	62.43	**78.29**	**77.11**
Central (%)	4.34	4.93	3.42	3.73
Distal (%)	19.27	26.01	16.12	22.01
Peripheral (%)	34.46	31.48	**58.76**	**51.36**
Exhaled Fraction (%)	16.72	13.33	5.18	3.83
D/P Ratio	0.56	0.83	0.27	0.43
(C+D)/P Ratio	0.69	0.98	0.33	0.50

Legend: Extra thoracic = mouth and upper airway; Intrathoracic = passed the larynx; Central = trachea + main bronchus; Distal = airways beyond main bronchus visible in a CT scan; Peripheral = passed the airways visible in a CT scan; D/P ratio = ratio between Distal and Peripheral deposition; (C+D)/P ratio = ratio between (Central + Distal) and peripheral deposition;. CF patient data: male, 46 years old, 171cm height, FEV1 1,73L (47%); NCFB patient data: female, 77 years old, 173cm height, FEV1 0,9L (32%).

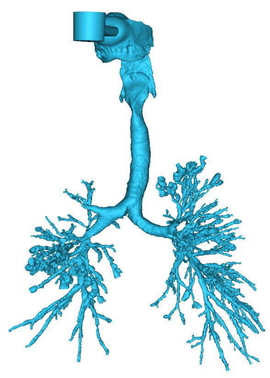

Figure 3 - Reverse engineered CT scan of Kolibri virtually coupled to the mouth of a CF patient

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Conclusion

In *in-silico* studies, both in healthy and diseased lung models, the realistic Kolibri™ guided breathing profile showed a more favourable pattern for deep lung deposition when compared to a spontaneous unguided breathing profile.

Realistic breathing profiles, based on real patient data, can provide more accurate and representative data regarding regional lung deposition, ultimately reducing risks during drug development by early optimization of pulmonary drug delivery.

References:

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