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A PREDICTIVE PLATFORM FOR HUMAN LUNG PHARMACOKINETICS OF INHALED BIOTHERAPEUTIC PROTEINS

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ABSTRACT

Protein-based medications are deposited, absorbed, distributed, maintained, and removed from the respiratory system using a predictive tool for human lung pharmacokinetics (PK) of inhaled biotherapeutic proteins. To precisely forecast drug absorption and distribution, the platform makes use of lung physiology, aerosol deposition characteristics, physiologically based pharmacokinetic (PBPK) models, and protein-specific characteristics including molecular weight, stability, and permeability. This approach minimizes animal research and streamlines human preclinical application. It is possible to enhance the simple formulation design, breathing device, and dosing schedule. This platform speeds up the creation of safe, efficient, and tailored inhaled biotherapeutic proteins for pulmonary infections, COPD, asthma, and cystic fibrosis.

Keywords: *Physiologically Based Pharmacokinetic (PBPK) Modeling; Human Lung Pharmacokinetics; Inhaled Biotherapeutic Proteins; Pulmonary Drug Delivery; Aerosol Deposition*

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1. INTRODUCTION

The pulmonary route is an effective way to administer biotherapeutic proteins because it targets the lungs, works fast, and has fewer side effects. Asthma, lung cancer, cystic fibrosis, pulmonary infections, and COPD can all be treated with inhaled monoclonal antibodies, enzymes, cytokines, and peptides. The creation of inhaled biotherapeutics is challenging due to the intricate relationships between aerosol deposition, mucus barriers, enzyme breakdown, protein stability, and pulmonary clearance pathways. Medication distribution and lung medicine efficacy prediction are challenging due to these features. This is due to the frequent variations in PK profiles.

Inhaled biotherapeutic protein pharmacokinetics prediction systems simulate inhaled protein pathways after treatment using physiological data, experimental data, and computer modeling to show how protein therapeutics are absorbed, distributed, broken down, and eliminated in the pulmonary PBPK models, CFD, in vitro permeability studies, and preclinical in vivo data. The absorption, deposition, passage through epithelial cells, and mucociliary cell cleaning of pulmonary medications are all examined by these prediction models. Product design, breathing assistance, and dose procedure enhancements prior to human testing are made possible by this integrated plan.

In order to expedite the transfer of inhaled biotherapeutic proteins from laboratory to clinic, strength prediction techniques are becoming increasingly important. By minimizing animal testing, accurate lung pharmacokinetic prediction lowers development costs, expedites the selection of candidates and formulations, and enhances clinical success.

2. MODEL DEVELOPMENT

The work used rhIFN-α1b as a model protein and used in vitro aerosol analysis, MPPD simulations, and PBPK modeling to predict the lung behavior of inhaled therapeutic proteins. The processes were aerosol

characterisation, pulmonary accumulation projection, mouse PBPK model creation, and application to healthy persons from various species.

In vitro aerosol performance characterization

A jet nebulizer (PARI TurboBOY) was used to test RhIFN-α1b injection (Sinovac Biopharmaceuticals) at 15, 30, 45, and 60 µg/mL. Facemask and mouthpiece tests assessed aerosol effectiveness. Aerosols were described using three complimentary methods:

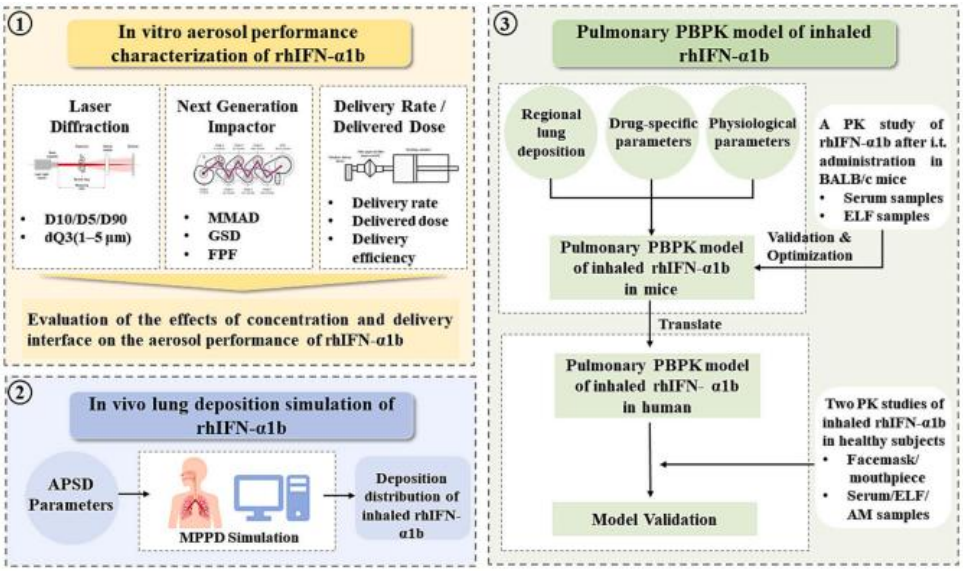

Fig. 1. Flowchart of this study.

- The geometric particle size distribution was determined by analyzing the median particle diameter (D50) and the proportion of particles between 1 and 5 µm (dQ3, 1–5 µm) using laser diffraction.
- The NGI study studied MMAD, GSD, and FPF aerodynamics. The nebulizer's aerosol delivery rate, total dose, efficiency, and residual volume were measured by a respiratory simulator.

The double-antibody sandwich ELISA showed 10–640 pg/mL of medication in each sample. Three studies were analyzed using GraphPad Prism for one-way or two-way ANOVA. P-values below 0.05 indicated significance.

MPPD-based prediction of pulmonary deposition

The MPPD program (version 3.04) simulated the distribution of inhaled rhIFN-α1b in the lungs. Model data came from MMAD and GSD trials. Simulations used the adult Weibel airway model. Tidal volume of 500 mL, respiratory rate of 15 breaths per minute, functional residual capacity of 3300 mL, and inspiration-expiration ratio of 1:1 were normal. The mouthpiece mimicked oral inhaling, while the facemask mimicked nasal and oral breathing. The model split 23 generations of airway deposition fractions into alveolar (17–23), lower (10–16), and higher (0–9) groups. The PBPK model detected area deposition fractions.

Pulmonary PBPK model development in mice

BALB/c mice modeled entire lung PBPK. Plasma, interstitial, and endothelial endosomes occur in all organs except the lungs. Plasma, capillary endosomes, interstitial space, and ELF compartments were found in upper, lower, and alveolar airways. Modeling capillaries, lymphatic drainage, nonspecific endocytosis, IFNAR-mediated uptake, epithelial transport, alveolar macrophage clearance, and target-mediated drug disposal. Adding physiological factors, receptor density, and drug-specific dynamics to literature. R package rxode2 includes differential equations.

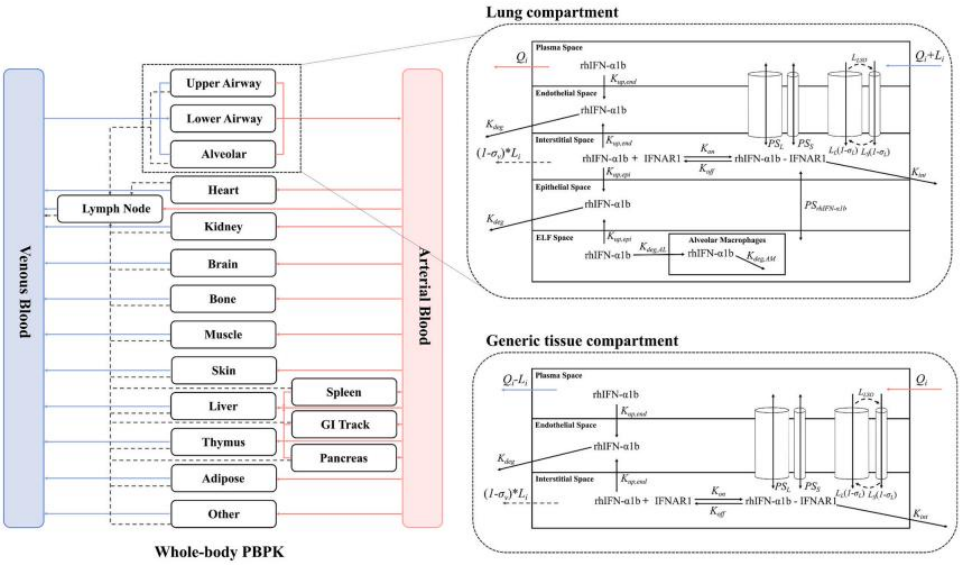

Figure 2: Structure of the Pulmonary Physiologically Based Pharmacokinetic (PBPK) Model for IFN-α1b.

Model validation and optimization

RhIFN-α1b (23.7 µg/kg) was given to female BALB/c mice (8-10 weeks old, 20 ± 2 g) via trachea utilizing a new aerosol technique. Blood and BALF were drawn 0.25–12 hours after injection. ELISA measured rhIFN-α1b levels, while ELF matches BALF quantities with urea data. In PBPK, MPPD predicted deposition fractions. Serum pharmacokinetics determined systemic clearance (CLv), while ELF concentration profiles refined epithelial and endothelial absorption.

Sensitivity analysis

A local sensitivity research examined how physiological and drug-specific variables affected lung and body exposure. Alveolar degradation, receptor binding affinity, epithelial permeability, endosomal degradation, systemic clearance, and absorption changed 50%. The model's sensitivity was assessed by examining serum and ELF AUC_0–∞ percentage changes.

Translation to the adult pulmonary PBPK model

The tested mouse PBPK model was applied to healthy individuals using mouse physiological features instead of human data to ensure optimal absorption. The addition of an alveolar macrophage component showed macrophage clearance, while allometric scaling showed system-wide clearance. The lung has three airways: alveolar (17–23 generations), lower (10–16 generations), and upper (0–9 generations), according to Weibel. The physiological features were acquired from ICRP databases and physiological pharmacokinetics literature.

Clinical model validation

The adult PBPK model was verified by analyzing pharmacokinetic data from healthy adults inhaling nebulized rhIFN-α1b via mouthpiece or facemask. Comparing serum, epithelial lining fluid, and alveolar macrophages to model predictions. The model was effective with Cmax and AUC_2–∞ ratios between 0.5 and 2.0. It predicted systemic and lung exposure from different inhalation methods and levels.

3. EXPERIMENTAL RESULTS

Aerosol Characterization of Nebulized rhIFN-α1b

At 15-60 µg/mL dosages, nebulized rhIFN-α1b particle size distribution matched aerosol studies. MMAD, GSD, and FPF remained consistent despite particle size distribution alterations. When medication concentration increased, the mouthpiece delivered aerosols less efficiently than the facemask. The mouthpiece supplied lung medication better than the facemask.

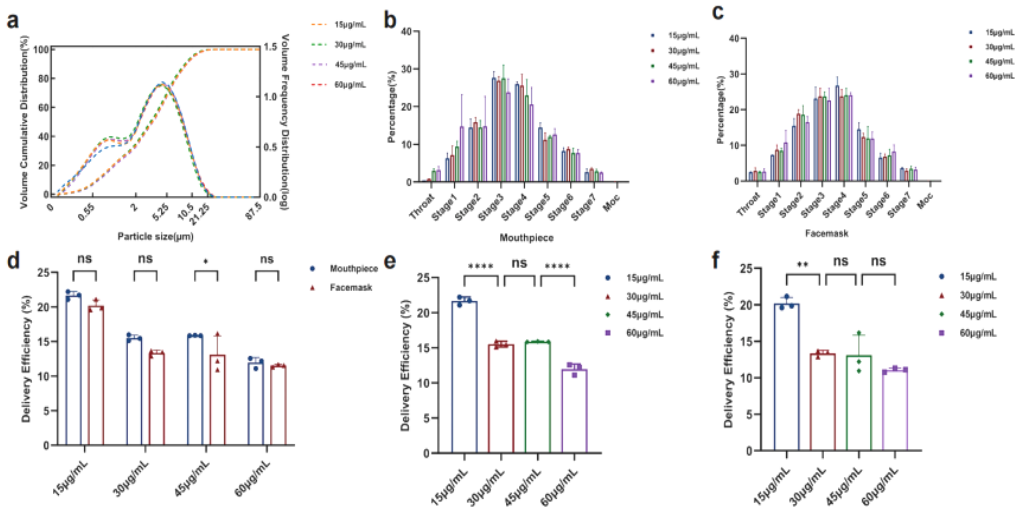

Fig. 3. Evaluation of the aerosol delivery performance of IFN-α1b.

Pulmonary Deposition Prediction of Nebulized rhIFN-α1b

The MPP models demonstrated regional lung deposition discrepancies amongst breathing devices. Compare to the facemask, the mouthpiece increased alveolar and lower airway drug deposition and decreased oropharynx drug deposition. Mouthpiece alveolar deposition was 1.5 times higher than facemask, indicating better peripheral lung targeting and drug administration.

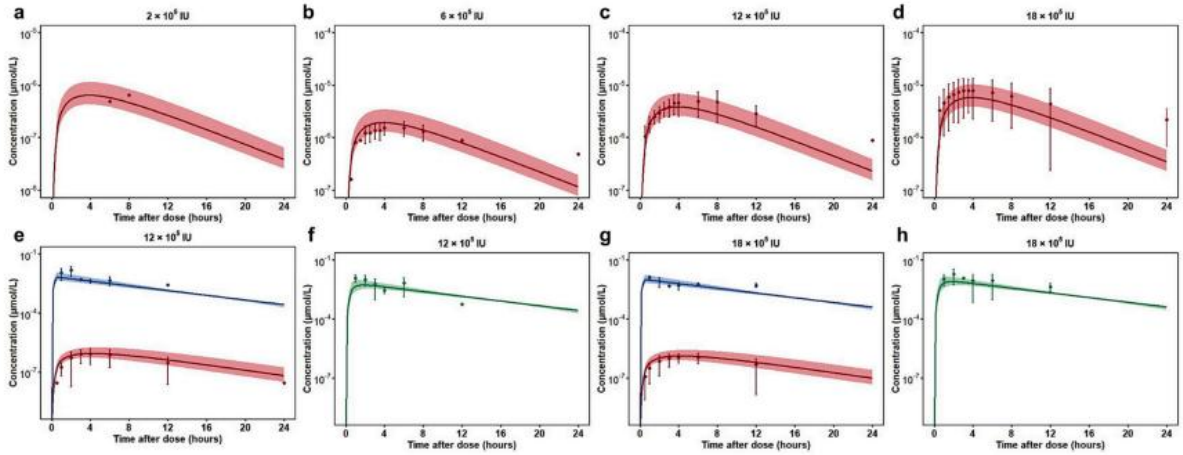

Fig. 4. Predicted pharmacokinetic profiles of IFN-α1b using the adult pulmonary PBPK model.

Pulmonary PBPK Model of Inhaled rhIFN-α1b in Mice

The mouse lung PBPK model accurately reflected rhIFN-α1b pharmacokinetics in serum and ELF. Systemic clearance and epithelial/endothelial uptake parameters matched experimental data after model adjustment. In sensitivity trials, CLv controlled systemic drug and ELF exposure via alveolar breakdown and epithelial absorption.

Pulmonary PBPK Model of Inhaled rhIFN-α1b in Healthy Adults

The adult pulmonary PBPK model accurately predicted RhIFN-α1b levels in blood, ELF, and alveolar macrophages after mouthpiece and facemask inhalation. Around 85% of predicted Cmax and AUC_0–∞ values matched clinical pharmacokinetic profiles at 0.5-2.0-fold dosages. Healthy adults' systemic and pulmonary exposure is reliably predicted by the model.

4. CONCLUSION

Human lung pharmacokinetics prediction tool for inhaled biotherapeutic proteins provides a solid PBPK framework for pulmonary distribution research. The model estimates inhaled protein pharmacokinetics using molecular properties such localized lung deposition, absorption, dispersion, cellular uptake, and systemic

exposure. Dose adjustment, formulation design, and human translation from preclinical research improve safe and effective inhalation biotherapeutic protein drug development without animal testing.

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