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Precision dosimetry in pulmonary drug delivery

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Nanotechnology-based platforms are being explored for the delivery of therapeutics directly to the lungs through inhalation. However, to ensure translational relevance between preclinical animal models and human applications, it is essential to accurately quantify and report the lung-deposited dose, rather than relying solely on the nominally administered dose.

Inhaled drug delivery enables targeted treatment of primary respiratory disorders and systemic diseases with pulmonary involvement. Inhalation therapy via aerosol delivery to the lungs involves a multi-step process comprising nominal dose administration, aerosol transport and deposition, and subsequent drug–lung interactions (Fig. 1a). However, the complex architecture of the respiratory tract, including the upper airways and the hierarchically branching lower airways, poses a major barrier to efficient deposition of therapeutic aerosols, particularly in the alveolar regions of the lungs. Consequently, therapeutic or toxicological outcomes are determined by the lung-deposited dose, rather than the nominally administered dose[1].

The lung-deposited dose is defined as the actual drug quantity deposited on lung tissue. Accordingly, delivery efficiency can be quantified as the lung-deposited dose normalized by the nominal dose. Measuring and reporting the lung-deposited dose are thus key to assessing delivery efficiency and drug efficacy as well as to ensuring reproducibility of dose–response relationships. Therefore, alongside immunological endpoints, such as antibody titers, T cell activation and antigen-presenting cell induction[2,3], lung-deposited dose should be routinely reported. Correlating lung-deposited dose to drug-targeted or transfected lung cell populations[2,4] would further clarify dose–response relationships. However, current low-resolution optical imaging approaches provide only semi-quantitative data with limited insight into lung-deposited dose and delivery efficiency[2,4].

Factors that influence lung-deposited dose

To deliver therapeutics to the lungs, a nominal amount of drug in liquid or dry powder form is typically loaded into inhaler devices that release a therapeutic aerosol dose, which is carried by airflow through tubing or delivery augmentation systems (for example, aerosol holding chambers or masks) to the nostrils or mouth. The fraction of aerosol that reaches the entrance of the respiratory system is referred to as the inhaled dose, which then travels through the upper airways to reach the lungs. The fraction that successfully deposits within the pulmonary region constitutes the lung-deposited dose (Fig. 1a).

The lung-deposited dose can be derived from the nominal dose if all contributing factors are considered. This includes the released fraction, which depends on internal losses within the delivery device and inhalation flow rates that determine aerosol size distribution. The lung-deposited dose is further affected by the respiratory profile (for example, slow-deep versus fast-shallow breathing) and species-specific lung anatomy.

Assessing lung-deposited dose

Imaging has a vital role in evaluating pulmonary drug delivery and deposition (Fig. 1b). In vivo and ex vivo fluorescence or bioluminescence imaging offer a gross view of drug distribution; however, their low resolution and tissue autofluorescence hinder accurate dose quantification. Nuclear imaging methods, such as gamma scintigraphy, single-photon emission computed tomography and positron emission tomography, enable quantitative assessment but suffer from limited spatial resolution and might require co-registration with computed tomography or magnetic resonance imaging for anatomical context. Nanoparticles and extracellular vesicles can be labelled with radionuclides or spiked with radiotracers to assess lung-deposited dose[5]; however, their routine application remains limited owing to stability issues, short isotope half-lives and high costs.

Different types of nanoparticle require distinct methods to quantify the lung-deposited dose; lipid nanoparticles require high-performance liquid chromatography[6] or liquid chromatography–mass spectrometry; protein-conjugated extracellular vesicles can be assessed using enzyme-linked immunosorbent assay[5]; and fluorophore-labelled nanoparticles can be measured by spectrofluorometry[7]. These destructive methods rely on tissue homogenates and require tissue extraction immediately post-administration to ensure accurate lung-deposited dose measurement before metabolic drug degradation.

Spatial distribution

Regional targeting is essential in the treatment of respiratory diseases, as site-specific delivery determines efficacy. For example, vaccines require deposition in the airway epithelium to trigger mucosal immunity, whereas therapies for lung fibrosis must reach deep alveolar regions. Spatial drug distribution is often underassessed and typically estimated using the penetration index (central-to-peripheral deposition ratio), as measured by gamma scintigraphy[8]. Tissue-cleared light sheet fluorescence microscopy enables cellular-level mapping of drug deposition in intact mouse lungs. Moreover, artificial intelligence (AI)-based tools, such as nnU-Net, enable precise segmentation of lung airways and spatial quantification of bronchial versus alveolar doses[7] (Fig. 1a).

Importantly, bulk liquid-based delivery methods typically favour central bronchial deposition, whereas aerosol inhalation achieves more uniform and peripheral alveolar drug distribution[7]. The effect of spatial patterns on therapeutic efficacy and toxicity remains unclear.

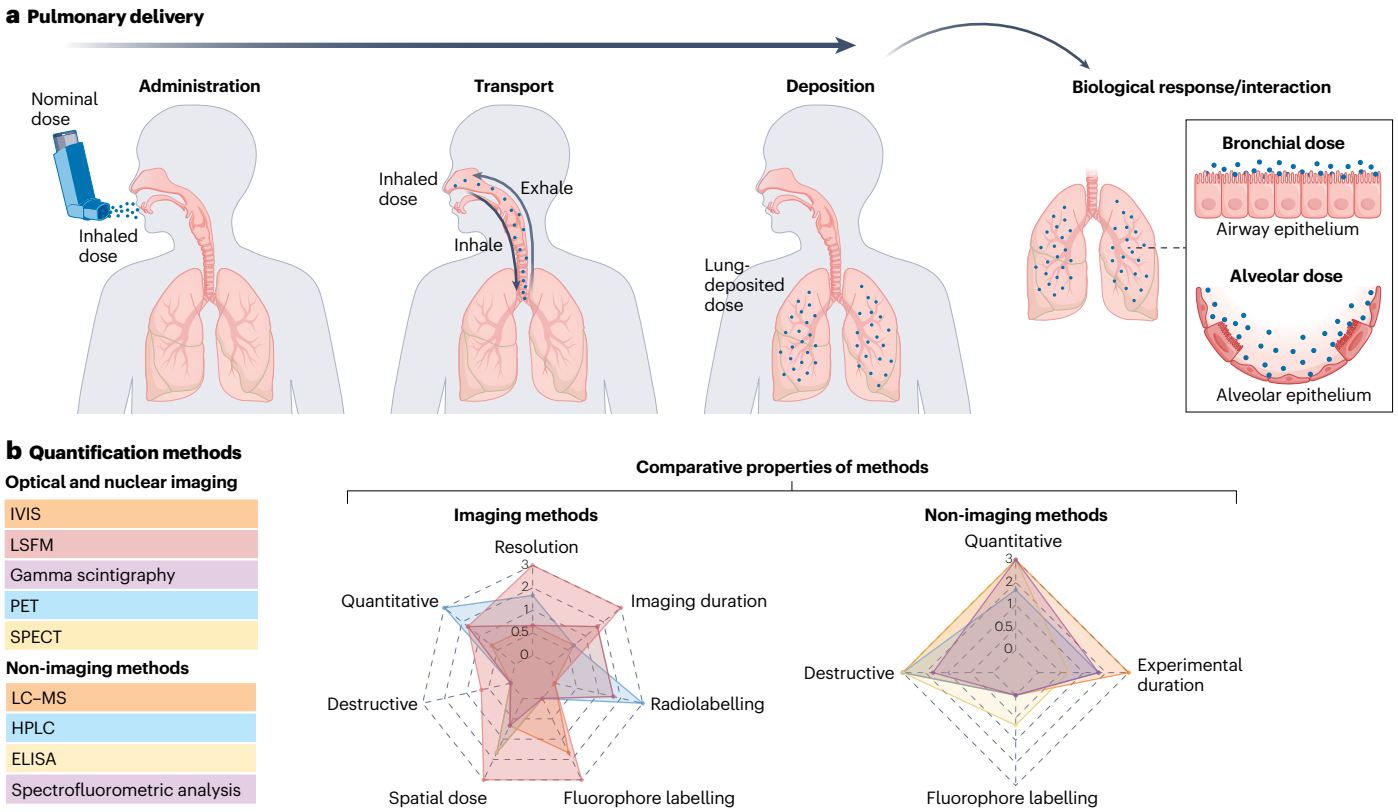

Fig. 1 | Precision dosimetry bridges preclinical and clinical development of inhalable drugs. a, Pulmonary drug inhalation encompasses a multistep process, from nominal dose administration to airway transport and lung deposition, emphasizing the lung-deposited dose as a key determinant of therapeutic outcomes. **b**, Imaging and non-imaging methods enable the visualization and quantification of the spatial distribution and dose of inhaled drugs. **c**, Translational considerations include lung disease pathophysiology, allometric scaling of lung-deposited dose and interspecies response scaling to enable accurate preclinical-to-clinical dose conversion. ELISA, enzyme-linked immunosorbent assay; HPLC, high-performance liquid chromatography; IVIS, in vivo imaging system; LC–MS, liquid chromatography–mass spectrometry; LDD, lung-deposited dose; LSFM, light sheet fluroescence microscopy; PET, positron emission tomography; SPECT, single photon emission computed tomography.

Spatial deposition and dosimetry are influenced by many factors, such as breathing pattern and disease state, but remain underexplored.

Implications for pulmonary delivery design

To accurately determine and maximize lung-deposited dose in nanotechnology-enabled pulmonary drug delivery, such as mRNA or drugs delivered by lipid nanoparticles[4] or extracellular vesicles[3,6], it is important to consider nanocarrier characteristics, such as size, composition, density and surface properties, and also aerosol attributes, including aerosolized-drug stability, delivery device, output rate, aerosol size distribution and inhalation protocols. Notably, aerosol administration via nose-only[4] or whole-body[3] exposures yield low delivery efficiencies of ≤0.2%[7]. Ventilator-assisted aerosol delivery achieves a higher delivery efficiency (around 4%)[7], primarily owing to direct tracheal aerosol delivery and optimized inhalation protocols. By contrast, liquid-based administration methods, such as intranasal aspiration and intratracheal instillation, offer higher delivery efficiencies (30% and 60%, respectively)[7] in animal models; however, their clinical relevance is limited. In addition, lung diseases and pathophysiological conditions, such as airway obstruction or narrowing in chronic obstructive

pulmonary disease, should be accounted for, as they influence aerosol dynamics and deposition (Fig. 1c).

Translational relevance of lung dosimetry

Lung-deposited dose and associated parameters (such as inhaled dose or spatial dose) are crucial to align therapeutic outcomes across species. Translation relies on allometric scaling to normalize lung-deposited dose to body weight, lung volume and alveolar epithelial surface area (Fig. 1c), accounting for interspecies differences in lung anatomy and physiology[9]. Animal models, such as rodents, dogs, cows and rhesus macaques, possess distinct lung structures[4,5], which can lead to substantial variation in lung-deposited dose, even if nominal or inhaled doses are matched by body weight or lung volume[9].

If direct measurement of lung-deposited dose is unfeasible, the inhaled dose from the specific delivery device should be reported, as aerosol output and transport losses can vary substantially across inhalation platforms and protocols. In line with this, the updated European Respiratory Society standard for methacholine challenge testing[10] recommends the use of inhaled rather than nominal doses to ensure consistency and comparability across delivery devices and protocols. Importantly, allometric lung-deposited dose and interspecies response scaling should be included in preclinical designs to improve translational accuracy, optimize dosing strategies and reduce the risk of adverse effects (Fig. 1c).

Toward precision inhalation therapy

Standardizing dosimetry reporting across preclinical studies is indispensable to improve the reproducibility and comparability of pulmonary delivery approaches and promote therapeutic optimization and regulatory approval. Machine learning tools may assist in predicting deposition patterns across devices, formulations and disease states. Lung-deposited dose optimization and spatial delivery can transition pulmonary drug delivery from poorly dose-controlled, empirically validated formulations to precision therapeutics.

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Author contributions

L.Y. and C.C. conceived the idea. L.Y. drafted the manuscript and designed the figure with support from O.S. and C.C. L.H. contributed to the synopsis and created the figure. All authors discussed, revised and approved the final version.

Competing interests

The authors declare no competing interests.