Quantitative detection of drug dose and spatial distribution in the lung revealed by Cryoslicing Imaging.

Abstract:
Administration of drugs via inhalation is an attractive route for pulmonary and systemic drug delivery. The therapeutic outcome of inhalation therapy depends not only on the dose of the lung-delivered drug, but also on its bioactivity and regional distribution. Fluorescence imaging has the potential to monitor these aspects already during preclinical development of inhaled drugs, but quantitative methods of analysis are lacking. In this proof-of-concept study, we demonstrate that Cryoslicing Imaging allows for 3D quantitative fluorescence imaging on ex vivo murine lungs. Known amounts of fluorescent substance (nanoparticles or fluorophore-drug conjugate) were instilled in the lungs of mice. The excised lungs were measured by Cryoslicing Imaging. Herein, white light and fluorescence images are obtained from the face of a gradually sliced frozen organ block. A quantitative representation of the fluorescence intensity throughout the lung was inferred from the images by accounting for instrument noise, tissue autofluorescence and out-of-plane fluorescence. Importantly, the out-of-plane fluorescence correction is based on the experimentally determined effective light attenuation coefficient of frozen murine lung tissue (10.0 ± 0.6 cm⁻¹ at 716 nm).
linear correlation between pulmonary total fluorescence intensity and pulmonary fluorophore dose indicates the validity of this method and allows direct fluorophore dose assessment. The pulmonary dose of a fluorescence-labeled drug (Fc?R-Alexa750) could be assessed with an estimated accuracy of 9% and the limit of detection in ng regime. Hence, Cryoslicing Imaging can be used for quantitative assessment of dose and 3D distribution of fluorescence-labeled drugs or drug carriers in the lungs of mice.

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