Pre-clinical optical molecular imaging in the lung: technological challenges and future prospects

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In recent years, the fledgling field of small animal fluorescence molecular imaging has enabled great advances in pre-clinical research, driven by the development of both new optical imaging modalities at the macroscopic and microscopic scales (1), and novel classes of targeted imaging probes that report on the molecular status of cells and target tissues with exquisite specificity (2). In combination, these developments have uniquely enabled non-invasive visualization of patterns of gene expression and molecular profiles of cells during disease development and in response to new types of therapeutics for a range of diseases. Despite this great progress, relatively very few pre-clinical fluorescence molecular imaging studies of *thoracic* disease have been reported in the literature compared to other widely studied disease models such as cancer (3) and cardiovascular disease (4). At the heart of the issue are substantial technical challenges associated with optical imaging in the lung. A full review of these challenges is beyond the scope of this editorial, but broadly speaking they may be classified into two areas; development of optical instrumentation suited for unique aspects of lung imaging and discovery of new molecular probes specific to thoracic diseases.

The lung is an extremely difficult organ to image optically. Nearly all biological tissue is, by nature, highly scattering to red and near-infrared light. For example, in breast tissue, a photon may travel a mean distance 10 cm before being absorbed, but only 100 μm before being scattered. However, even by these standards, light scattering in the lung is extremely high. Recent studies of the optical properties of the mouse chest cavities showed that the optical properties of the lungs in mice are 2-3 times greater than nearby organs such as the heart or liver (5) since the micro-structure of the lung includes strong optical heterogeneity, e.g., between alveolar walls and the gases within, which leads to severe scattering and refraction as photons traverse the lung. Thus macroscopic three-dimensional imaging techniques such as fluorescence molecular tomography (FMT) have yet to achieve their full potential resolution capabilities in the lung. In recent years, substantial improvement has been facilitated by advanced imaging methods, including time-gated detection of early-arriving (minimally scattered) photons from an ultra-fast laser through bulk tissue volumes (6) or the use of hybrid multi-modality imaging techniques, wherein data from high resolution structural imaging modalities (such as X-ray Computed Tomography) guide FMT reconstruction (1). Nevertheless, continued development of new macroscopic fluorescence imaging technologies is greatly needed to allow researchers studying thoracic disease in small animal models and to leverage the power of fluorescence molecular imaging.

The challenges are equally daunting, and opportunities equally vast, at the microscopic scale wherein researchers wish to observe, for example, changes in micro-structure (e.g., atelectasis or mechanical indentation (7) to study lung collapse and re-inflation) or the infiltration of hematopoietic cells in response to disease or injury (8). The initial problem is, of course, avoiding deflation of the lung while surgically obtaining access to it. To address this concern, specialized *in vivo* experimental preparations have been developed that allow exposure of the lung through an optical window while keeping the lung ventilated and the animal alive (9). Through this, confocal, multi-photon, and second-harmonic microscopy can image a few micrometers with sub-septal resolution, and optical coherence tomography (OCT; sometimes referred to as the "optical analog of ultrasound") can image collapse and re-inflation of one layer of sub-pleural alveoli *in situ*, and has provided the first i*n-vivo* 3D images of individual alveoli (10). These images can suffer distortions such as underestimation of alveolar volume, so algorithms are being developed to correct them (11), but validation of the results against *ex-vivo* "ground truth" is also difficult because the

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lung collapses under biopsy and fixation or freezing of inflated lung can alter its micro-structure. Liquid-filled lung has limited physiological relevance, but is easier to image and may facilitate validation. Computational models (12) and lung phantoms (11) partially compensate for the lack of validation in physiological specimens.

In addition to optical imaging technologies, development of new fluorescence molecular probes specific to thoracic disease and injury represent a vast potential area of future research growth. While the past decade has witnessed design and validation of an extensive library of fluorescent molecular probes to image, for example, cancer (3) - i.e. cancer related genes, cell surface receptors and enzymes - relatively few have been developed for clinically important thoracic conditions such as asthma, chronic obstructive pulmonary disorder, pulmonary fibrosis, acute lung injury and others. In response to this, the National Heart Lung and Blood Institute of the US National Institutes of Health recently established a special funding program in part to stimulate development of molecular imaging probes specific to the lung (13). It is likely that improved optical imaging techniques will drive development of improved molecular probes in the future, and vice-versa.

While optical molecular imaging holds great promise for aiding our understanding of the development, progression and management of many thoracic diseases through pre-clinical research, improved technology is required to harness this potential fully. Given the scope of the thoracic disease in human health globally, it is critical that scientists, engineers, clinicians and funding agencies continue to support and grow this important area of research worldwide.

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