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Molecular Imaging of Biological Samples in Pharmaceutical Development Using Mass Spectrometry Imaging and Machine Learning

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Drug molecules are designed to reach a target site of action at a sufficient concentration to deliver efficacy. Understanding the distribution, metabolism and accumulation of drug in the body is a key challenge in pharmaceutical research and development. Traditionally, plasma or homogenized tissue samples are characterized for this purpose. However, these measurements do not provide molecular distribution information for tissues or cells within a specific organ. Radio-labelled technologies, such as quantitative whole-body autoradiography (qWBA), are utilized to study drug distributions. Despite the success of label-based imaging technologies, there is a significant interest in the development of label-free targeted and untargeted imaging modalities. Mass spectrometry imaging (MSI) is a powerful label-free molecular imaging technique, which enables simultaneous localization of drugs, metabolites, lipids, and proteins in tissue sections with high sensitivity and unprecedented molecular specificity [1]. MSI technologies usually utilize a laser beam, cluster beam, or liquid stream to desorb and ionize analytes. Subsequentially, a mixture of ionized analytes is analyzed by a mass spectrometer. After four decades of development of both sampling and acquisition, MSI enables mapping hundreds of molecules in a single experiment at sub-cellular resolution. To efficiently analyze the vast MSI data, many machine learning approaches have been developed for data mining and visualization [2].

We will present a suite of analytical methods, which combines MSI and machine learning to quantify molecular distributions and analyze biochemical pathways in tissues. A spatial segmentation method has been developed to localize distinct cell types and visualize molecular heterogeneity of tissues based on MSI data. This type of digital pathology enables accurate quantification of molecules in specific tissue subregions [3]. In addition, a self-supervised clustering approach has been developed to autonomously classify molecules with respect to their spatial distributions using convolutional neural networks. Identification of these functionally related molecules helps analyze biochemical pathways in the tissue [4]. We will demonstrate their applications to study glucuronidation of drugs in mouse kidney [5]. Herein, diclofenac was selected as a model drug. We characterized drug, drug metabolites, and endogenous molecules in mouse kidney. We quantified diclofenac acyl glucuronide in the medulla region to evaluate the excretion of this toxic drug metabolite. We also identified endogenous metabolites and lipids co-localized with drug and drug metabolites, which enables further investigation of drug metabolism pathways. These applications highlight the potential of MSI to tackle technical challenges in pharmaceutical research and development.

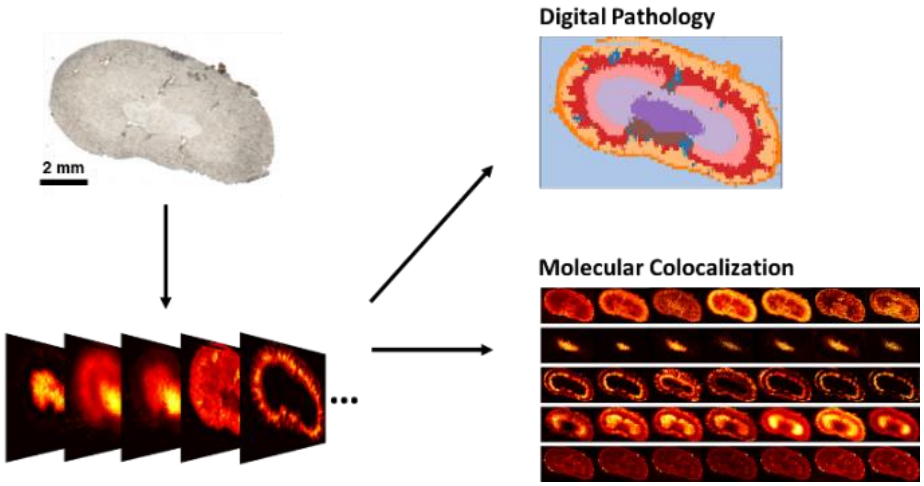

Figure 1. An example workflow to perform digital pathology and study molecular colocalization in mouse kidney tissue using mass spectrometry imaging and machine learning approaches.

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