

## **High-resolution Imaging of Biological Samples Using Nanospray Desorption Electrospray Ionization (nano-DESI) Mass Spectrometry**

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Mass spectrometry imaging (MSI) enables detailed molecular mapping of biological samples with high sensitivity and molecular specificity. The highly-multiplexed imaging using MSI is ideally suited for studying the localization of hundreds of lipids and metabolites in biological samples in a single experiment. We have developed an MSI technique based on nanospray desorption electrospray ionization (nano-DESI). Nano-DESI is an ambient ionization technique that relies on localized liquid extraction of analyte molecules from the sample into a dynamic liquid bridge formed between the nano-DESI probe and sample surface. The extracted analytes are transferred to a mass spectrometer inlet and ionized by electrospray ionization. The high sensitivity of nano-DESI enables imaging with high spatial resolution of 8-10 microns, which opens new directions for the molecular profiling of individual cells in heterogeneous biological tissues and understanding the role of the tissue microenvironment on cellular function. Meanwhile, the solvent composition may be adjusted to further enhance the sensitivity and molecular coverage of nano-DESI MSI or to enable on-the-fly derivatization. In particular, we have developed approaches for imaging of isomeric lipids by converting them into hydroperoxides using a reaction with singlet oxygen. In these experiments, singlet oxygen is produced by adding a photosensitizer to the extraction solvent and irradiating the extracted mixture using a laser pointer. This capability will advance our understanding of the role of isomeric lipids in health and disease. We have also developed an approach for imaging of intact individual proteoforms in tissues. Nano-DESI MSI generates multiply charged protein ions, which makes it possible to use top-down proteomics approaches for their identification. The ability to perform high-resolution imaging of lipids and metabolites first and then intact proteins in the same sample is particularly advantageous for obtaining the most detailed molecular maps of biological systems. Furthermore, imaging of proteins facilitates data integration with immunofluorescence imaging and other imaging modalities. These developments have established high-resolution nano-DESI MSI as a powerful technique for studying biological systems.