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RESOLVING MOLECULAR COMPLEXITY IN IMAGING WITH FT-ICR MASS SPECTROMETRY

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Cellular interactions within the tissue microenvironment underpin health and disease. Exposure to nutrients, toxins, and neighboring cells triggers coordinated molecular responses that shape cellular function and metabolism in beneficial, adaptive, or detrimental ways. Acquiring molecular information at cellular resolution is therefore critical for developing a comprehensive understanding of biological systems. Matrix-assisted laser desorption/ionization (MALDI) imaging mass spectrometry (IMS) addresses this need by combining the spatial fidelity of classical microscopy with the molecular specificity of mass spectrometry. However, a central challenge in molecular imaging remains the need for improved molecular coverage, sensitivity, and confidence in molecular identification.

Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometry is uniquely suited to address these challenges due to its unmatched mass resolving power and mass accuracy. In the context of direct tissue analysis, where thousands of chemically diverse species are sampled simultaneously from discrete spatial locations, this ultra-high resolving capability is essential for disentangling isobaric and isomeric interferences and enabling confident molecular assignments.

Here, I will present our work developing and applying FT-ICR-based IMS technologies, with an emphasis on instrumental strategies to improve spatial resolution, molecular coverage, dynamic range, and peak annotation. Early efforts demonstrated the potential of FT-ICR for spatially resolved analysis of intact proteins, enabling direct mapping of proteoforms in tissue with high mass accuracy and specificity. In parallel, trap-based platforms provide unique opportunities for gas-phase fractionation, effectively increasing the dynamic range of MALDI IMS measurements and enabling detection of lower-abundance species in the presence of highly abundant molecular backgrounds. I will highlight our work in this area for lipid and metabolite imaging.

Finally, I will present ongoing efforts to advance FT-ICR for molecular imaging through the development of next-generation instrumentation and workflows that integrate high-spatial-resolution sampling with ultra-high-resolution mass analysis. These approaches aim to overcome traditional trade-offs between spatial resolution, sensitivity, and spectral performance, enabling more comprehensive molecular characterization at increasingly finer spatial scales.

FT-ICR MS remains a powerful platform for advancing spatial molecular biology, enabling detailed characterization of cellular microenvironments and providing new insights into the molecular mechanisms underlying human health and disease.

Key words:
Imaging Mass Spectrometry, Spatial Biology, HRMS, infectious disease