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3D NanoSIMS: a novel high-mass resolution instrument for 3D molecular imaging with sub-micron resolution

Ian GILMORE*

NiCE-MSI, National Physical Laboratory, UK

ian.gilmore@npl.co.uk

The pharmaceutical industry is facing many challenges through the increasing cost of bringing a drug to market and the reducing size of patient groups. Drugs that fail at late stage have the largest burden of cost and therefore it is essential to identify failure early. The challenge here is to measure where drugs go at the intra-cellular level to answer long-standing questions about whether drug concentrations are sufficiently high in the right places to have a therapeutic effect, or if the medicine is lodging within cellular components and causing toxicity. If anomalies were spotted earlier it could explain toxicities or lack of efficacy. Secondary ion mass spectrometry (SIMS) has great potential but current instruments lack the sensitivity, spatial- and mass-resolution.

We have developed a powerful new hybrid SIMS instrument combining an OrbitrapTM-based Thermo ScientificTM Q ExactiveTM HF instrument and a dedicated ToF-SIMS 5 analyser. The instrument is equipped with high-resolution ion beams including a new micron resolution argon cluster ion beam for biomolecular imaging and 3D analysis of organics and an ultra-high resolution Bi cluster focussed ion beam with < 80 nm resolution. The ToF analyser allows high-speed imaging needed for 3D analysis and the High Field Orbitrap analyser allows high-mass resolution, mass accuracy and MS/MS for chemical identification. The instrument is designed for life-sciences applications including sub-cellular 3D imaging of metabolites, imaging of bacteria and biofilms and imaging of medical devices with complex topographies that confound traditional instrument designs.

We show data demonstrating the unique advantages of this novel instrument. Imaging with large argon clusters provides rich biomolecular spectra including intact lipids and metabolites. However, results in state-of-the-art instruments are limited to a mass resolving power of around 6,000 which is insufficient to allow unique identification. We show images of mouse brain with a sub-cellular spatial resolution of less than 2 microns simultaneously with a mass resolving power of over 100,000 for intact lipids. We fully separate the (3'-sulfo)Gal-Cer(d18:1/24:1(2-OH)) and (3'-sulfo)Gal-Cer(d18:1/25:0) sulfatides, which reveals a difference in spatial distribution. In the low mass region, mass resolving powers of >400,000 are achieved allowing clear separation of the low abundance metabolite dopamine from other peaks. We show the ability to image the drug amiodarone with sub-cellular resolution and show that the mass spectra are not affected by sample topography. A further important benefit is the ability to image in 3D with high-efficiency taking advantage of the high-speed ToF analyser for imaging and using the Orbitrap analyser to detect ions during the sputtering cycle (normally not collected in ToF analysers) enabling both an increase in sensitivity and high-mass resolving power. This is exemplified with model nanostructured multilayer samples and organic electronic materials.

All animal studies were ethically reviewed and carried out in accordance with Animals (Scientific Procedures) Act 1986