Title: Multiplexed screening of thousands of natural products for protein-ligand binding in native mass spectrometry

Abstract:

The structural diversity of natural products offers unique opportunities for drug discovery, providing an unrivalled source of complex chemical scaffolds that can be adapted to afford highly selective pharmaceutical agents. Unfortunately, the utilization of natural products as a source of lead compounds in drug discovery has significantly declined over the past 30 years, in part due to the challenges associated with screening complex natural product extracts to identify bioactive small molecules. The development of new methods for natural product screening should promote a resurgence in natural product drug discovery and facilitate the identification of novel small molecule therapeutics. In this talk I will introduce a mass spectrometry-based approach that integrates untargeted metabolomics with multistage, high-resolution native mass spectrometry to rapidly identify natural products that bind to therapeutically relevant protein targets. By combining nanoscale ion emitters with low-volume gel filtration in native mass spectrometry, baseline-resolved protein-ligand complexes could be formed and detected from crude natural product extracts containing thousands of drug-like small molecules. Furthermore, by employing a multistage ion activation approach across a broad mass range, bound ligands could be confidently identified without the need for fractionation. By applying this approach to a range of soluble proteins of interest, two novel natural product ligands of human drug targets were identified. This method should significantly increase the efficiency of target-based natural product drug discovery workflows without the requirement for specialized robotics and detection systems. Furthermore, the direct screening of complex mixtures using the approach outlined could be integrated into more fundamental biological challenges, including the identification of endogenous protein ligands.