

Journal club



ORIGINS OF MASS SPECTROMETRY-BASED PROTEOMICS

Mass spectrometry (MS), which was already a cornerstone of analytical chemistry in the twentieth century, had been confined to a niche role in molecular biology owing to its inability to ionize and vaporize labile molecules such as proteins. This changed dramatically in 1989 with the introduction of electrospray ionization for the analysis of intact proteins, in which I was fortunate to be involved, and which led to the 2002 Nobel Prize in Chemistry for my thesis advisor John Fenn. On a mission to bring MS to ‘real biology’ when I started my own group at the EMBL in Heidelberg, Germany, I was fascinated by a 1992 *Science* paper by the group of Donald Hunt, which clearly showed that this was no fantasy.

Using electrospray ionization, Hunt *et al.* had developed an online liquid chromatography (LC)–MS

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set-up that was based on ultra-narrow columns and capable of sequencing femtomole amounts of peptides from complex mixtures. This was far beyond the capabilities of the chemical peptide-sequencing methods, such as Edman degradation, in use at the time. Unlike ‘artificial’ MS studies of purified and diluted-down peptides, Hunt and colleagues had taken on a real biological challenge — the detection of peptides presented to the immune system. This first large-scale analysis of MHC class I-bound peptides yielded 19 (partially) sequenced peptides, but hinted at the existence of hundreds more. In continuing collaboration with the group of Victor Engelhard, the Hunt group went on to solve many problems concerned with antigen presentation by MHC molecules — an area that is as hot as ever owing to the recent breakthroughs in immuno-oncology.

This electrospray nano-LC–MS/MS platform was further fortified with efficient database searching using MS/MS spectra — which was introduced shortly afterwards by

John Yates from the Hunt group and, simultaneously, by my fledgling group — and this technique remains at the heart of MS-based proteomics. In the intervening 25 years, the amazing analytical performance demonstrated in Hunt’s paper has been further improved at least 1,000-fold in terms of sensitivity, throughput and complexity, with no signs of this progress slowing down.

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The author declares no competing interests.

ORIGINAL ARTICLES Hunt, D. F. *et al.*

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