

# MASS SPECTROMETRY DRIVEN BIOLOGICAL DISCOVERY

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Large-scale protein biochemistry or proteomics emerged from the convergence of large-scale sequencing of genomes and high sensitivity mass spectrometry. As the sequencing of the Human genome and the genomes of model organisms was contemplated in the late 1980's, the field of mass spectrometry experienced a dramatic shift in capability with the development of electrospray ionization (ESI) and matrix-assisted laser desorption/ionization. ESI enabled a long sought after method to directly and robustly introduce the effluent from HPLC's into the mass spectrometer. Coupled with the capability of tandem mass spectrometers to select and fragment peptides, a powerful approach to sequence peptides and subsequently proteins was developed. The combination of ESI and microscale HPLC created significant improvements in the sensitivity of detection and decreased the quantity of protein required for sequencing experiments. A key element to drive the use of LC/MS/MS to large-scale analysis was the development of computational algorithms to compare tandem mass spectrometry data of peptides to the sequences of an organism to identify amino acid sequences. Algorithms to compare sequences to spectra and determine closeness of fit have enabled large-scale experiments by simplifying and automating data analysis. These methods unleashed the power for tandem mass spectrometers for mixture analysis and in particular enabled the analysis of proteolytically digested protein mixtures. By combining high resolution separation techniques such as 1 or 2-dimensional HPLC with tandem mass spectrometry complex biological structures can be studied. This approach to protein biochemistry has been termed "shotgun proteomics" when applied to mixtures of proteins. By using these techniques protein complexes, organelles, cells and tissues have been analyzed providing a new analytical paradigm to study biological systems. Selected examples that place into context the functions of proteins from biological structures will be discussed.