A Mass Spec Timeline

Stu Borman,
Hailey Russell, and
Gary Siuzdak

Developing techniques to measure mass has been a Nobel pursuit.

Mass spectrometry has a dynamic history dotted with Nobel laureates and a continually advancing technology that has made significant inroads into drug discovery, protein characterization, and even disease diagnosis. The history of the science clearly shows that MS had its roots in physics, branched into chemistry, and in the past two decades, has budded into biology.

The Physical Roots

The history of MS begins with Sir Joseph John Thomson of the University of Cambridge. Thomson's "theoretical and experimental investigations on the conduction of electricity by gases" led to the discovery of the electron in 1897, for which Thomson was awarded the 1906 Nobel Prize in Physics (*1*). In the first decade of the 20th century, Thomson went on to construct the first mass spectrometer (then called a parabola spectrograph), in which ions were separated by their different parabolic trajectories in electromagnetic fields and detection occurred by the ions striking a fluorescent screen or photographic plate (Figure 1, *2*).

In the years just after World War I, Thomson's University of Cambridge protégé, Francis W. Aston (1922 Nobel Prize in Chemistry), designed a mass spectrometer that improved the resolving power by an order of magnitude, allowing Aston to study isotopes. During this same period, A. J. Dempster of the University of Chicago also improved on resolution with a magnetic analyzer and developed the first electron impact source, which ionizes volatilized molecules with a beam of electrons. Electron impact ion sources are still widely used in modern mass spectrometers for small-molecule analysis.

Thomson, Aston, and Dempster built a strong foundation of MS theory and instrument design, making it possible for those who followed to develop instruments capable of meeting the demands of chemists and biologists. The task of building such instruments, however, required six decades of effort.

Chemical Branches

One of the great concerns, particularly for chemists, was creating an instrument with enough accuracy for the analysis of both the elements and small organic molecules. The answer to this problem would come in four different forms: magnetic sector double-focusing, time-of-flight (TOF), quadrupole, and Fourier transform ion cyclotron resonance (FT-ICR) mass analyzers. Alfred O. C. Nier at the University of Minnesota developed the high-mass-resolution double-focusing instrument during World War II to perform isotopic analysis and separate ^{235}U from ^{238}U (*3*). In fact, the first nuclear bomb was developed entirely from the uranium separated by this type of mass spectrometer.

William E. Stephens of the University of Pennsylvania proposed the concept of TOF MS in 1946 (*4*). In a TOF analyzer, ions are separated on the basis of differences in their velocities as they move in a straight path toward a collector. TOF MS is fast, capable of high resolving power and high accuracy, and applicable to chromatographic detection, and it is used for the mass determination of large biomolecules because of its virtually limitless mass range.

First reported in the mid-1950s by Wolfgang Paul of the University of Bonn, the quadrupole mass filter (*5*) has proved to be ideal for coupling to GC and, more recently, LC. In such a device, a quadrupolar electrical field (comprising radiofrequency and direct-current components) was used to separate ions. Paul later shared the Nobel Prize in Physics for his work on ion trapping.

Although quadrupole mass spectrometers were not as accurate or precise as double-focusing instruments, they offered excellent dynamic range, were quite stable, and were also readily applied to tandem MS experiments—features that make them popular for quantitative analysis and drug discovery applications (*6*).

For the ultimate solution to high resolution and high accuracy, however, ICR MS has been the most successful mass analysis technique. Initially described by J. A. Hipple and colleagues, ICR operates by subjecting ions simultaneously to a radio frequency electric field and a uniform magnetic field, causing the ions to follow spiral paths in an analyzer chamber (*7*). By scanning the radio frequency or magnetic field, researchers could detect the ions sequentially. In 1974, Melvin B. Comisarow and Alan G. Marshall of the University of British Columbia revolutionized ICR by developing FT-ICR MS (*8*). The major advantage of FT-ICR MS was that it allowed many different ions to be measured at once, and sub-part-per-million-accuracy is now

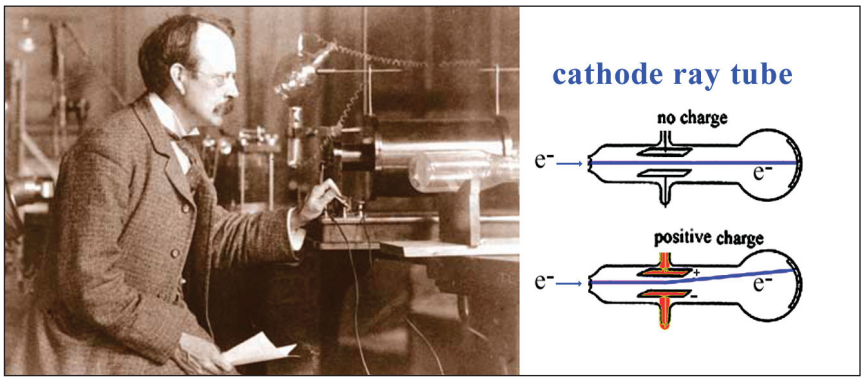

FIGURE 1: J. J. Thomson and a cathode ray tube used to perform some of the first *m/z* measurements. Deflection of the electron was observed once the electric field was turned on.

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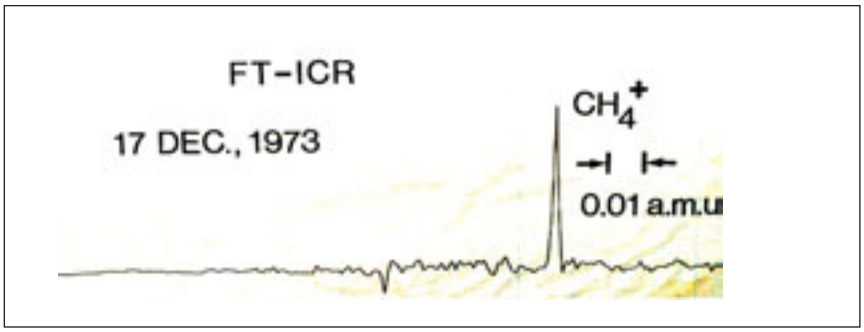

FIGURE 2: First FT-ICR mass spectrum, courtesy of Alan G. Marshall.

routinely possible with commercial instruments (Figure 2).

All of these mass analyzer designs—and even combinations of different techniques for tandem MS—are still used today and are continually being developed for new applications.

Budding into Biology

Despite advances in mass accuracy, mass range, quantitative analysis, and the ability to couple the instruments to chromatography, by the 1980s, MS still lacked efficacy for large- and small-biomolecule analysis. Significant molecular decomposition or fragmentation during vaporization/ionization and poor sensitivity proved problematic. The application of "soft ionization" electrospray ionization (ESI) and matrix-assisted laser desorption/ionization (MALDI) allowed MS to evolve into the realm of biology.

In ESI MS, highly charged droplets dispersed from a capillary in an electric field were evaporated, and the resulting ions were drawn into an MS inlet. Although chemistry professor Malcolm Dole of Northwestern University first conceived the technique in the 1960s, it was not until the early 1980s that John B. Fenn of Yale University put it into practice for biomolecule analysis. Koichi Tanaka and co-workers at Shimadzu Corp. initially reported MALDI MS, which was also developed by Franz Hillenkamp and Michael Karas at the University of Frankfurt. In MALDI, analyte molecules are laser-desorbed from a solid or liquid UV-absorbing matrix.

For their work on developing soft ionization techniques suitable for large-biomolecule analysis, Fenn and Tanaka shared the 2002 Nobel Prize in Chemistry. ESI and MALDI have made MS increasingly useful for sophisticated biological experiments, such as the sequencing and analysis of peptides and proteins using techniques pioneered by Klaus Biemann of the Massachusetts Institute of Technology; studies of noncovalent complexes and immunological molecules; DNA sequencing; and the analysis of intact viruses (Figure 3).

Toward Whole-Organism Analysis

Of course, MS continues to evolve, and the importance of these past developments is evident in the research efforts at every major pharmaceutical company and university in the world today. Arguably the two most important applications that drove these developments are in pharmacokinetics for small-molecule drug analysis and protein identification using "peptide mass mapping" (*9*). Recently, the analysis of small endogenous biomolecules by MS has also found its way into clinical studies, where it is currently used as a rapid and inexpensive neonatal screen for more than 30 different diseases (*10*).

Soft ionization methods have been important in the majority of biologically relevant work. Recent efforts by Brian Chait at Rockefeller University to develop MS methods to study noncovalent interactions have clearly demonstrated the method's utility in studying protein–protein complexes or even in examining subcellular components (*11*, *12*). In fact, novel ESI instrumentation has made it possible to generate

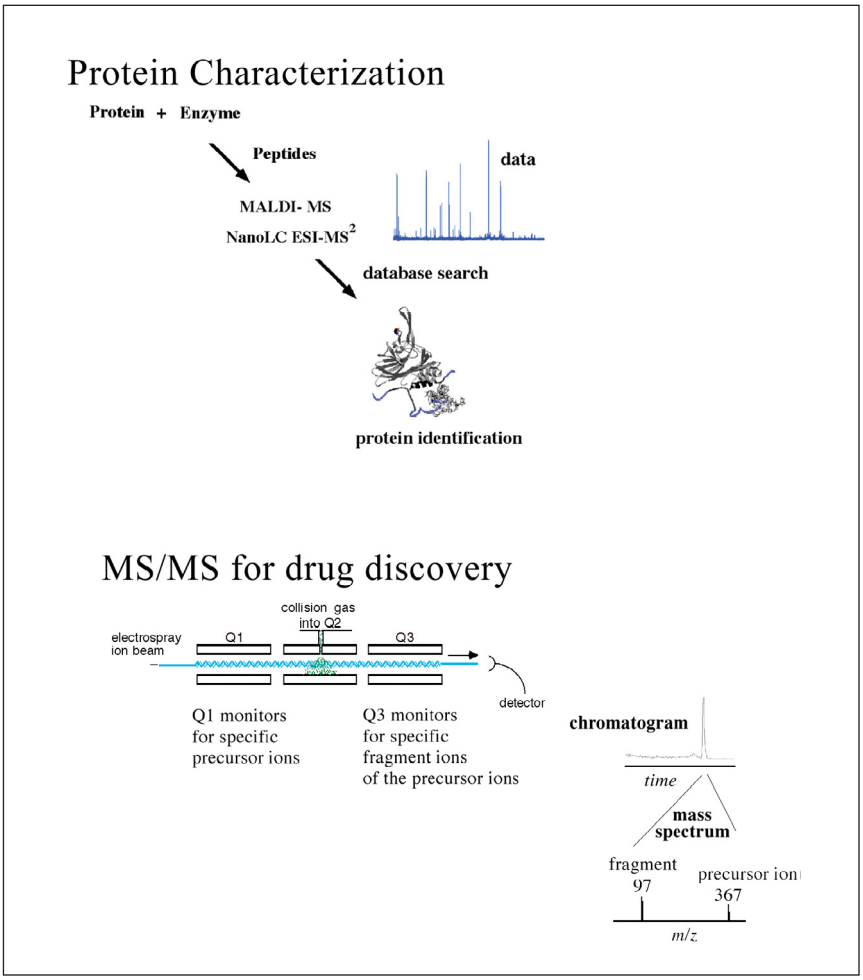

FIGURE 3: MALDI and nanoLC ESI tandem MS strategies are routinely used for protein identification (top). ESI tandem MS is also widely used for disease diagnosis in neonatal screening (bottom). Schematic courtesy of Gary Siuzdak.

Table 1. Historical Developments in MS

Investigator(s)	Year	Contribution
Thomson	1899–1911	First mass spectrometer
Dempster	1918	Electron ionization and magnetic focusing
Aston	1919	Atomic weights using MS
Stephens	1946	Time-of-flight mass analysis
Hipple, Sommer, and Thomas	1949	Ion cyclotron resonance
Johnson and Nier	1953	Double-focusing instruments
Paul and Steinwedel	1953	Quadrupole analyzers
Beynon	1956	High-resolution MS
Biemann, Cone, Webster, and Arsenault	1966	Peptide sequencing
Munson and Field	1966	Chemical ionization
Dole	1968	Electrospray ionization
Beckey	1969	Field desorption MS of organic molecules
MacFarlane and Torgerson	1974	Plasma desorption MS
Comisarow and Marshall	1974	FT-ICR MS
Yost and Enke	1978	Triple quadrupole MS
Barber	1981	Fast atom bombardment (FAB)
Tanaka, Karas, and Hillenkamp	1983	Matrix-assisted laser desorption/ionization
Fenn	1984	ESI on biomolecules
Chowdhury, Katta, and Chait	1990	Protein conformational changes with ESI MS
Mann and Wilm	1991	MicroESI
Ganem, Li, and Henion Chait and Katta	1991	Noncovalent complexes with ESI MS
Pieles, Zurcher, Schär, and Moser	1993	Oligonucleotide ladder sequencing
Henzel, Billeci, Stults, Wong, Grimley, and Watanabe	1993	Protein mass mapping
Siuzdak, Bothner, Fuerstenau, and Benner	1996–2001	Intact viral analysis

intact viral ions measuring millions of daltons and to show that virus structure and virulence are preserved (*13, 14*).

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Stu Borman *is a senior correspondent with* Chemical & Engineering News *(http://pubs.acs.org/cen),* **Hailey Russell** *is a research scientist at the Scripps Research Institute (www.scripps.edu), and* **Gary Siuzdak** *is an associate professor of molecular biology and director of the Scripps Center for Mass Spectrometry (http://masspec.scripps.edu). Send your comments or questions about this article to tcaw@acs.org or to the Editorial Office address on page 3.* ◆