Mass Spectrometry–Based Protein Biomarker Discovery: Solving the Remaining Challenges to Reach the Promise of Clinical Benefit

Lance A. Liotta1* and Emanuel F. Petricoin1


This report in The Lancet generated a great deal of excitement about the application of mass spectrometry (MS) to discover candidate protein biomarkers for early-stage ovarian cancer. MS-based serum/plasma biomarker profiling was launched in a flourish of optimism to meet the urgent need for biomarkers of early-stage cancer, a need that still exists today. Before 1998, very few investigators used MS (MALDI-TOF or electrospray ionization) to directly analyze blood, because serum was considered too complex and “dirty” for direct introduction into expensive and sophisticated MS research instruments. The door was opened to the use of MS for biomarker research in 1998 with SELDI, a new modification of MALDI-TOF technology. Researchers were immediately intrigued by the SELDI-TOF approach because body fluids could be applied directly to the chip surface and then analyzed to generate an ion fingerprint (1, 2). SELDI had relatively low resolution and could not identify the ions directly. Nevertheless, it provided a fresh approach in the search for the ion signatures of hundreds of candidate biomarkers. We saw SELDI-TOF as a means to test a new hypothesis that was emerging in the protein biomarker field. Investigators had proposed that tumor–host interactions in the tissue microenvironment were generating cascades of biomarkers. A corollary of the hypothesis was that a panel of biomarkers could achieve diagnostic sensitivity and specificity superior to those of previously failed one-at-a-time searches for cancer biomarkers.

We used SELDI to reveal the protein fingerprints of candidate disease biomarkers in sera from patients with early-stage ovarian cancer. The analysis achieved apparently high diagnostic sensitivity and specificity in blinded test sets. Despite the initial excitement generated by this publication, translating this research into reliable clinical tests has been the difficult part. That is often the case when research tools are asked to perform in a clinical diagnostic setting. Although the SELDI platform itself was not suitable for routine clinical diagnostics, this platform “broke the ice” with respect to the use of MS to discover panels of candidate disease biomarkers (1, 2). Indeed, some of the ion peaks discovered with SELDI that were described in our original Lancet report have been sequenced and identified in a study that used an independent set of ovarian cancer sera (3). These results revealed the biological importance and platform independence of the ion patterns we initially discovered. Importantly, the affirmation of our hypothesis in the original Lancet report is exemplified by the recent clearance by the US Food and Drug Administration of a series of markers originally identified with SELDI in the Chan laboratory (2).

To move research biomarkers to the bedside, we need to render the diagnostic biomarker readout independent of the measurement platform. The biology—and the biomarkers themselves—should remain independent of the changing MS technology. Sequencing and identifying the proteins that are the source of the MS diagnostic peaks cause the output to be independent of the measurement platform, because the analytes can be measured with any suitable immunoassay or analytical system, now or in the future.

Despite the rapid advances in the application of MS to biomarker discovery, serious physiologic challenges remain. Cancer-associated biomarkers in blood exist at exceedingly low concentrations within complex mixtures of high-abundance proteins, such as albumin and immunoglobulins. Moreover, biomarkers in the blood may degrade during transportation and storage. The analytical sensitivity of MS for discovering biomarkers in blood is actually very low. The vast majority of the hundreds of clinical analytes routinely measured in the clinical chemistry laboratory today cannot be detected with the current MS technology (4), a sobering reality for de novo discovery efforts, given our hopes for finding new markers.

1 Center for Applied Proteomics and Molecular Medicine, George Mason University, Manassas, VA.
* Address correspondence to this author at: George Mason University, 10900 University Blvd., Discovery Hall, MS 4E3, Manassas, VA 20110. Fax 703-993-4288; e-mail lliotta@gmu.edu.
Received April 30, 2010; accepted May 6, 2010.
Previously published online at DOI: 10.1373/clinchem.2010.146142
2 This report has been cited more than 1530 times since publication.
Fortunately, advances in nanotechnology are providing a completely new approach for increasing the detection capabilities of MS for biomarker discovery. We have created a new technology, a nanoparticle for biomarker “harvesting” that rapidly concentrates and amplifies low-abundance proteins for MS, multiple reaction monitoring, or immunoassay-based analysis. The technology has been documented to increase the detection limit of MS and immunoassays by \( \times 100 \)-fold without increasing the background signal (5). With such advances, optimism is again surging that MS-based discovery and measurement will soon yield its promise to the clinic.

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

Authors’ Disclosures of Potential Conflicts of Interest: Upon manuscript submission, all authors completed the Disclosures of Potential Conflict of Interest form. Potential conflicts of interest:

Employment or Leadership: None declared.

Consultant or Advisory Role: L.A. Liotta, Ceres Nanosciences; E.F. Petricoin, Ceres Nanosciences.


Honoraria: None declared.

Research Funding: None declared.

Expert Testimony: None declared.

Role of Sponsor: The funding organizations played no role in the design of study, choice of enrolled patients, review and interpretation of data, or preparation or approval of manuscript.

References


