



FINAL THOUGHTS

April 2008

FUELING PROTEOMIC DIAGNOSTICS

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As the notion of cancer as a manageable disease begins to gain momentum, it becomes impossible to overestimate the value of early detection. Unfortunately, early detection remains elusive for many malignancies, and the typical breast cancer patient has had the disease for a decade by the time of diagnosis due to mammography's 70% sensitivity rate. Although magnetic resonance imaging is more sensitive and detects breast lesions much earlier than mammography, it is often prohibited by high costs and lack of availability.

Biomarkers hold the most promise for generating rapid, accurate, and reasonably priced early-stage cancer diagnostics. In theory, a sensitive biomarker-based test can detect a tumor before it becomes visible through physical examination or imaging. As a result, biomarkers have become indispensable in drug development, where clinical endpoints are frequently measured by the attainment of up- or down-regulated proteins, genes, or metabolites. Biomarkers may also serve as signals for a drug's effectiveness and may eventually fuel the growth of personalized medicine.

Although proteins are not the only biomarkers available for drug development, they offer the most accurate picture of a patient's health. Where genes illustrate the potential emergence of a disease phenotype, in the labyrinthine interplay of DNA, regulatory RNA and proteins, is often too complex for IVD developers to decipher. By contrast, proteins only aid in phenotype definition and therefore provide only the most essential material for IVD development.

Room for Growth

Protein biomarkers are not without their shortcomings. Protein concentrations have a wide dynamic range, measuring roughly 10¹⁰, which confounds the search for low-abundance protein biomarkers. The range also renders it difficult to compare two proteins with radically different concentrations.

Another hurdle facing protein biomarker diagnostics development is the relative lack of high-throughput techniques for measuring rising and falling protein levels. In this regard, genomics is several years ahead of proteomics as several whole-genome chips have already been commercialized. Currently, there is no equivalent analytic platform for the human proteome.

However, today's protein analytic technology is more than adequate for diagnostic purposes as long as IVD developers know what they are searching for. High-performance liquid chromatography and two-dimensional gel electrophoresis have successfully served protein chemists for decades, and mass spectroscopy has recently provided a high level of sensitivity for protein biomarker detection and characterization.

Another approach to the specificity and sensitivity dilemma is to increase the statistical power of single protein biomarkers by combining several biomarkers into a single assay, a technique with direct parallels in genomics- and metabolomics-based diagnostics. In such assays, some concentrations of proteins rise and others fall. Provided the model is valid, mathematical tools can be applied to provide a high level of statistical validity to the result.

In this scenario, disease phenotypes are identified by increases or decreases in protein concentrations for a panel in comparison with normal controls. Changes in a single protein may tell diagnosticians little, but differences among six or more proteins can provide tremendous insight. This approach provides the best opportunity to develop diagnostic products that directly influence patients' treatment.

To realize the potential of this idea, test developers will need better analytic tools. Specifically, developers of proteomics-based diagnostics require more-sensitive, resilient tools that are equipped with automated precision best suited for identifying and quantifying low-abundance proteins. IVD manufacturers also need mathematical methods to decipher complex data and high-throughput methods that rival the speed of geno-mic analysis.

In the future, human genome research is expected to generate tens of thousands of potential protein biomarkers implicated in human disease. Researchers, suppliers, and physicians must continue developing methods that will enable the mining of proteomic information, not only for diagnostics and therapy, but also for a deeper knowledge of human biology.

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