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Instant insight: Disease snapshots

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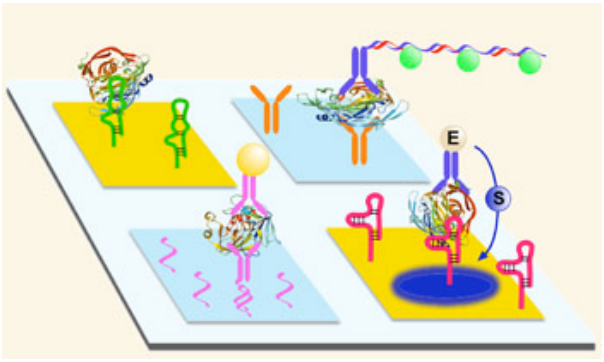
Hye Jin Lee, Alastair Wark and Robert Corn look at the latest breakthroughs in the use of microarray technology for the fast detection and treatment of cancer and other diseases

Detecting the presence of protein biomarkers in bodily fluids such as blood and urine offers a convenient route to critical information about the onset and progression of many types of diseases. Consequently, the discovery of new biomarkers is rapidly becoming an essential component of biomedical research with the goal of developing accurate tests that allow earlier detection and improve disease classification. With the end goal of developing a more targeted approach to patient therapy, and monitoring response to treatment.



Microarrays are used to detect protein biomarkers in blood and urine

However, the challenge of identifying and quantitatively measuring biomarkers, especially proteins, is a tough one. Many potential targets reside at concentrations several orders of magnitude lower than the most abundant proteins typically found in biological samples. Therefore, detection methods with both high sensitivity and specificity are needed. It is also becoming increasingly evident that complex diseases cannot be characterised through a single biomarker. Instead, large sets of proteins need to be screened simultaneously in an individual sample to reveal characteristic patterns where some proteins are over expressed and others strongly repressed compared to healthy patient samples. This will provide a more accurate assessment of the disease sub-type and the level of progression, where even small changes between different protein levels will be highly informative.

Underpinning the emergence of biomarker technology is the development of new proteomic tools alongside a concomitant effort by scientists to understand disease at the molecular level. The most relied upon methods for protein diagnostics include gel-electrophoresis, western blotting and enzyme-linked immunosorbent assays (ELISA). Over the last decade the utility of mass spectrometry for protein mixture analysis has also improved dramatically. However, none of these techniques are well-suited for the multiplexed analysis of many targets within an individual sample and typically lack the sensitivity necessary for fully resolving proteins present in biological samples at very low concentrations.

Microarray-based techniques, consisting of large numbers of biomolecular capture probes immobilised on a single substrate surface, have become the leading technique for the high-throughput monitoring of biomolecular interactions. Each capture probe has a high binding affinity towards a particular target biomolecule present in the sample solution. However, despite the widespread use of DNA microarrays, the application of protein microarrays has proven to be considerably more challenging. This is due to both a limited availability of biomarker capture probes and the surface immobilisation of these probes without subsequent loss in bioactivity. Most efforts have focused on the successful development of antibody microarray technology, but the issue of assay cross-reactivity especially as the number of probes and sample complexity increases still remains a fundamental hurdle. This has encouraged researchers to explore alternative biomolecular probes whose protein binding properties are similar to or better than those of antibodies. Examples include DNA and RNA aptamers, peptides and cell or tissue lysates that can be applied in an array format for protein biomarker measurements.

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"Undoubtedly, microarray technologies will play an increasingly important role in improving our understanding and treatment of disease"

In addition to improving specificity, rapid advances are being made in the development of signal amplification methodologies for detecting interactions between molecular probes and their protein targets. It is essential that these new technologies can be readily applied in an array format without compromising the integrity of neighbouring array elements. Novel surface-based enzymatic amplification reactions such as rolling circle amplification have been used to further lower detection limits. Advances in nanotechnology have also enabled more sensitive detection by labelling protein probe molecules with different types of nanoparticles that open up a variety of new optical, electrical and magnetic techniques for biomarker detection.

Undoubtedly, as improvements in design and application continue, microarray technologies will play an increasingly important role in improving our understanding and treatment of disease.

Read Hye Jin Lee, Alastair Wark and Robert Corn's Highlight 'Microarray methods for protein biomarker detection' in issue 8, 2008 of The Analyst

Link to journal article

Microarray methods for protein biomarker detection
Hye Jin Lee, Alastair W. Wark and Robert M. Corn, *Analyst*, 2008, **133**, 975
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