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# Trends in proteomics contract research

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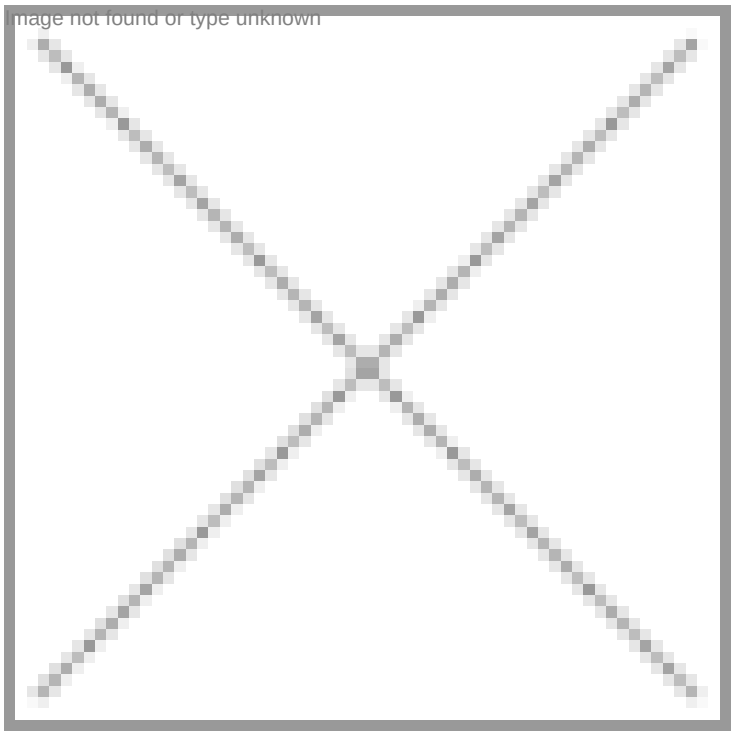

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*Dr Richard Lipscombe is the founder and Managing Director of Proteomics International, Australia and an expert in protein analysis. Proteomics International is both a contract service provider and research and development company, focusing on developing value from unlocking the protein code specifically for drug discovery and biological research. Dr Lipscomb is a protein chemist with extensive experience in analysing biomolecules using proteomics techniques. This includes over 20 years international experience in hospital and academic laboratories and in Australia, the US and the UK.*

Proteomics is analysing all the proteins in a cell, tissue or organism, or more simply, a system. Exemplifying the practical term of system, proteomics is used narrowly to study specific pathways within a cell, or broadly, with the example of the Human Liver Proteome Project centred in China, to map every protein involved in the operation of the second most complex organ in the human body.

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**Advancements in proteomics**

Most developments in proteomics and protein discovery have focused on a systems approach, and specifically system comparison and biomarker discovery. Applications are enormous, from human diseases such as cancer and diabetes, to salt tolerance and pathogen resistance in crops. This is achieved by comparative proteomics using a series of separation techniques followed by the identification power of the mass spectrometer. Sensitive mapping of many protein and peptide systems is possible â€“ 50 micrograms of protein extract from a cell culture can be sufficient to identify over 1000 proteins from that system, or a single scorpion sting can be mapped to identify over 300 new peptides (each a potential new drug). Whilst as little as 10 years ago, it was standard practice to identify one protein in 24 hours with Edman N-terminal protein sequencing, it is now possible to sequence and reliably identify one protein in one minute with a mass spectrometer.

Liquid chromatography (HPLC) has taken over from traditional two-dimensional gel electrophoresis as the method of choice for protein separation. The most successful techniques are based on the MudPIT (multidimensional protein identification technology) approach, which uses a series of chromatography steps (usually ion exchange and reverse phase) to separate a complex mixture of protein fragments. An essential step is that the entire protein sample is first digested into peptides before it is applied to the HPLC. This ultimately presents a bioinformatics challenge, but saves time because the sample (i.e., all the peptides) can be directly analysed by mass spectrometry.

In order to compare the differential protein expression of two or more samples, the proteins from each source can be chemically and uniquely labelled before the separation experiment begins. When successful, the comparative analysis produces new information on the key components of the system-discovering biomarkers for that disease or trait.

Current approaches seek to improve peptide separation and sensitivity, and an exciting development has been the advent of LC-MALDI MS (liquid chromatography - matrix assisted laser desorption ionisation mass spectrometry), whereby the HPLC eluates are mixed with matrix and simultaneously spotted onto MALDI MS targets. This has a number of advantages:, high-throughput TOF (time of flight) instruments can be used to process the samples; the samples are stable on the target so it can be archived and processed at a convenient time; the samples can be re-analysed.

The coverage obtained by the different proteome mapping methods varies, however, LC-MALDI and MudPIT LC/MS have clearly overtaken 2D-gel electrophoresis. Of course, no one approach will tell the whole story. Whichever system is used vast amounts of data are created â€“ nowadays one comparative protein discovery experiment can create nearly a 1Gb file. This requires extraordinary computing power, and centralised super computers that can handle the data of many groups are a sensible solution. The Australian Proteomics Computational Facility is one such example, accepting data from any group in the APAC region.

**Proteomics and contract research**

Interest in analysing protein systems in great detail has led to a focus on post translational modifications (PTMs) such as phosphorylation and redox changes of thiol groups. These PTMs allow whole new classes of protein activities to be targeted with exquisite selectivity. The techniques being developed also have another far-reaching benefit: to provide a new suite of tools for the fast emerging biosimilars market â€“ a precision approach to quality control. This rapidly growing market is forecast to be worth a heady 3,45,000 crore ($77 billion) within two years. Biosimilars, also termed biogenerics or follow-on biologics include monoclonal antibody type drugs, and novel medications like insulin, beta interferon, G-CSF and coagulation factors.

A growing role for protein analysis CRO's is to offer complete, independent, molecular characterization. This ranges from verification of amino acid sequence to disulphide bridging and ratification of PEGylation sites. Many techniques remain in their infancy in traditional analytical labs, whilst accredited facilities are extremely rare.

Agencies such as the FDA are starting to realise the power of this new application of proteomics, and are pressing forreliable mass spectrometry based data.
Regional testing authorities such as NATA (Australia), and APLAC (Asia Pacific Laboratory Accreditation Cooperation) are responding and it is probable that ISO/IEC 17025 laboratory standards will become an essential QC requirement for advanced proteomics facilities.

The broadening interest in proteins as therapeutic and agri-biochemical targets, or as diagnostic markers, means there are a wealth of projects to pursue, and numerous ways of pursuing them.

Appreciating the potential rewards, and the pitfalls, as researchers engage with contract service providers will ensure afaster path to that next protein discovery.

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