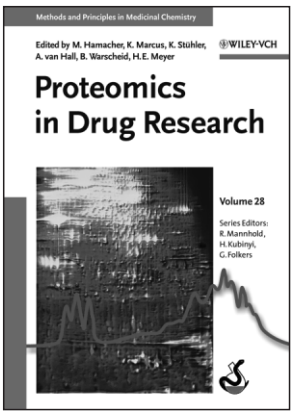
Books



Proteomics in Drug Research
Series: Methods and Principles in Medicinal Chemistry

Hamacher, M., Marcus, K., Stühler, K., van Hall, A., Warscheid, B. and Meyer, H. E. (Eds).
Wiley-VCH, Weinheim, Germany, 2006, pp 362
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The editors of this fine book are all from the Medical Proteome Center of Ruhr-University in Bochum, Germany. They have brought together experienced proteomics researchers to (i) address organizational and management aspects of collaborative, multidisciplinary research; (ii) authoritatively describe major technology platforms and bioinformatics methods essential for proteomics and peptidomics research; (iii) introduce less familiar assays, such as biomolecular interaction analyses and photonic microscopic robot technology for protein interactions; and (iv) identify potential applications to the discovery of biomarkers for patient stratification, earlier diagnosis, and targets for drug development. The key word is potential: there are very few examples of actual drugs whose discovery or development has already benefited from proteomics research. And few of the authors are from major pharmaceutical or biotechnology companies.

In the Preface, the editors challenge their colleagues to conduct 5 to 10 independent repetitions of experiments in a field where "one-off experiments" are often published and coefficients of variation are rare. They draw upon the German and HUPO Brain Proteome Projects to illustrate the necessity for standardization of methods and data submission and the challenges of networking and building consortia. The newer MS instruments (LTQ-FT, Orbitrap, triple-quad) and targeted proteomics strategies (labeled N-glycosite peptides, MRM) have appeared since this book was planned and drafted; this situation is inevitable in a rapidly advancing field like proteomics technology platforms. Nevertheless, sample processing remains a poorly-controlled variable. The available methods only partially explore the complexity, let alone the functionalities, of tissue and biofluid proteomes. And the throughput for analysis is inadequate for clinical trial and epidemiological research. Many proteins have multiple, seemingly unrelated activities, with pleiotropic effects on phenotypes.

Seven of the 17 chapters describe searches for drug candidates or biomarkers. Butt and Marcus boldly, perhaps exuberantly, state that "proteomics has entirely shifted the paradigm for drug discovery and novel diagnostics". That chapter describes 2-D PAGE + ^{32}P-autoradiography + MS to determine substrates of cAMP- and cGMP-dependent protein kinases and MAPK kinases affected by drugs that inhibit platelet aggregation. Drug candidates undergo modifications and have multiple actions, illustrated by leflunomide for rheumatoid arthritis using cell lines *in vitro*. Receptors and enzymes are the preferred drug targets, since they have routine, automated binding and enzyme inhibitor assays. Transport proteins, ion-channel proteins, and transcription factors require more complex assays. Other chapters examine resistance to mitoxantrone therapy in breast cancer MCF-7 cells, and markers for renal cell cancers. Altered ubiquitination is prominent in dilated cardiomyopathies with development of heart failure, and crystallins and tropomyosins are elevated in endomyocardial biopsies and serum of patients with acute rejection of heart transplants.

With all the caveats, there is little doubt that understanding structure and function of proteins and their isoforms, identifying differential expression of proteins, pathways, and regulatory networks, and devising large-scale high-throughput proteomic analysis will provide a better basis for targeted therapeutics and more reliable detection of toxicities than has been the case with small molecule chemistry in recent decades. So far, genomics and transcriptomics have flooded the pharmaceutical industry with novel targets that have been difficult to validate in a disease context. Proteomics should help map the relevance of these targets. Meanwhile, proteins, humanized antibodies, and bioactive peptides themselves are major classes of successful therapeutic agents.

A broad readership should find the book of interest. Perhaps the title would be clearer if it were "Development of Proteomics for Potential Applications in Drug Research".

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