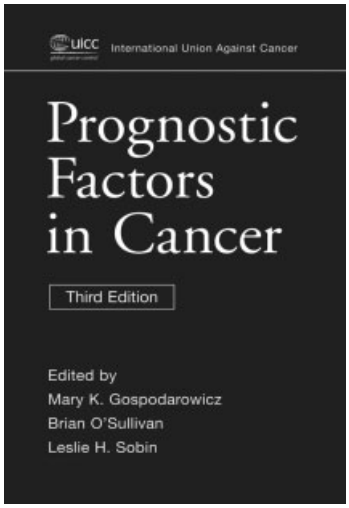
stra. The author summarizes the concepts, and discusses the problems relating to high-throughput protein identification and data analysis. Finally, in the last chapter, D. C. Liebler reviews bioinformatic tools for proteomics, notably for peptide sequence identification with MS data, the approaches for protein identification analysis of uninterpreted data, the role of software for *de novo* sequence interpretation from MS/MS data and presents other software packages used by the proteomic community.

In summary, the book is well structured and constructed, and globally, well written. The figures are of excellent quality. The book is highly recommended for all people, expert or not, who need simple, clear answers to common problems encountered in proteomics.

Professor Jean-Daniel Tissot
Service régional vaudois de transfusion sanguine
Lausanne, Switzerland

Prognostic Factors in Cancer, 3rd edition



M. K. Gospodarowicz, B. O'Sullivan, L. H. Sobin (Eds.)
Wiley-Liss, 2006, pp. 353
ISBN: 0-470-03801-2

This fresh edition of an established publication from the International Union Against Cancer (UICC) is both sobering and useful for proteomics. The book consists of six substantial chapters about principles of prognosis, and 39 brief chapters about as many different types of cancers, using a standardized format. The summary table for each tumor type provides a matrix of the tumor-related, host-related, and environmentally-related essential, additional, and promising prognostic factors that should be obtained for the patient and research records.

From the time of Hippocrates, prognosis was the physician's primary function, assisting patients to anticipate the likely outcomes of their disease. Since the emergence of modern diagnosis and therapies, prognosis has been neglected by physicians, say the various authors, despite its overriding importance for patients. "Diagnosis means generalizing, transcending the particular; prognosis. . .means individualizing" (cited, p. 5). Prognosis, in fact, is a key element of the vision many of us hold of predictive, personalized, and preventive (P3) healthcare.

What is sobering is how little from proteomics, or other molecular methods, has permeated oncology practice and clinical guidelines to date. "Proteomics" does not appear in the glossary, although "biomarker", "DNA arrays", and "molecular prognostic factor" do. "Protein-based prognostic factors" and "proteomics" make the index just twice. First, there is one page (p. 83–84) of general description, with 13 citations, a conclusion that no clinical integration of proteomic technology into prognostic classification systems has taken place (yet), but a projection that molecular characteristics will be incorporated into future prognostic systems. The second is a mere mention that "genomic- and proteomic-based studies have led to the identification of a large number of candidate biomarkers in prostate cancer" (p. 248). The only specific biomarkers highlighted are microvessel density and Ki-67, to be used in conjunction with TNM, prostate-specific antigen (PSA) level, and Gleason score. Likewise, it is sobering to read that a literature review of neuroblastoma noted 130 different markers investigated in 211 studies, with a median of one publication *per* marker. Cancers for which there is useful text about molecular prognostic factors are esophageal, colorectal, hepatocellular, pancreatic, lung (rather weak), breast (most extensive), endometrial, prostate, and non-Hodgkin lymphoma. Some authors distinguish prognostic (overall outcome) from predictive (response to therapy) applications.

The book will be useful to researchers designing studies using proteomics and panels of marker candidates to characterize heterogeneity of outcomes among patients with similar clinical, radiological, and histopathological features. Many papers already report molecular subgrouping of patients with big differences in Kaplan-Meier survival curves. Chapter 3 provides a good primer for design of study protocols, including exploratory (phase II) and confirmatory (phase III) studies and the risks of misleading results from failing to formulate

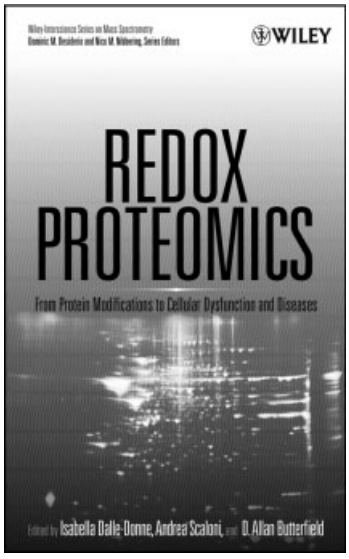
hypotheses, inadequate patient and event numbers, inappropriate multiple significance testing, overfitting regression models, and failing to verify with independent datasets. Guidelines for Reporting Tumor Marker Prognostic Studies (REMARK) are included. The clinical annotations provided to us must have detailed, credible TNM staging (T = tumor size or extent; N = tumor-bearing lymph nodes; M = metastatic lesions).

Protein biomarkers will be used to predict survival, disease-free interval, or quality of life in individuals already diagnosed (monitoring) and to screen undiagnosed individuals in the general population or subpopulations considered to be at-risk due to known exposures or precursor lesions. We should check that our clinical colleagues used the evidence-based "essential prognostic factors" in characterizing the patients and choosing the therapies. If the patients are not well-matched, including co-morbidities, differences correlated with molecular phenotypes may be misleading or add little value in a multivariate analysis. Conversely, adequate documentation will facilitate comparison of results, and meta-analyses, from different studies. The screening mode requires very high specificity and good sensitivity, in order to generate a useful positive predictive value; otherwise, most positive tests will be "false-positives". In contrast, the prognostic mode is focused on already-diagnosed patients, so the challenge lies in heterogeneity, not low prevalence. Finally, we should heed the distinction (p. 19) between predetermined prognosis and prognosis dependent upon later events. For example, an overall 50% long-term survival rate with a chemotherapy regimen might be due to differences already existing at the time of clinical evaluation, such that only 50% will respond at any dose, or might be due to therapy at the TCD50 concentration, so that patients might do a lot better at a higher dose, if tolerated.

Properly conducted clinical proteomics studies should add considerable value to both diagnosis and prognosis of cancers. Validated results may be feasible earlier for prognostic uses.

Gilbert S. Omenn
University of Michigan, USA

Redox Proteomics: From Protein Modifications to Cellular Dysfunction and Diseases



Isabella Dalle-Donne, Andrea Scaloni, A. Allan Butterfield (Eds.)
Wiley-Interscience Series on Mass Spectrometry,
Dominic M. Desiderio and Nico M. Nibbering (Series Eds.)
Wiley, 2006, pp. 944
ISBN: 0-471-72345-2

The human genome has been sequenced and protein-coding genes have been counted to be around 31,000 genes by the Human Genome Project. Those genes are thought to produce more than a million different proteins through both different mRNA splicing and various post-translational modifications, and protein expression with a $10^6 - 10^8$ dynamic range varies dynamically along the lifetime of a cell. We are now able to answer the question as to what genes really do, how molecular machineries are created and/or destroyed, and how they interplay as members of a biological system to make up life. Many cellular processes are performed and regulated not by individual proteins but by proteins acting in large protein assemblies or macromolecular complexes.

This 944-page book collectively covers the current understanding of chemical biology of oxidative stress and physiology, proteomic technologies, redox proteomics in normal cellular physiology and pharmacology, and proteomic applications to disease states. Numerous disease states and normal aging involve oxidative modification of proteins which would result in cellular dysfunction. Changes in the reductive or oxidative capacity of the cell lead to post-translational modification of proteins by reactive oxygen species (ROS) / reactive nitrogen species (RNS) *via* "redox cell signaling". Redox Proteomics focuses considerably on protein modifications and identifies oxidatively modified proteins in both a qualitative and quantitative manner in order to attain molecular mechanisms of cellular dysfunction and to investigate the effects of disease, metabolism, pharmacological agents, aging and so on.

The fundamental background of chemical protein modifications of biological systems under oxidative stress are comprehensively and educationally introduced in the early chapters. Varieties of methodological developments revised for proteomic research are referred to, including multidimensional protein identification technology (MudPIT) and isotope-coded affinity tag (ICAT), to identify and quantify oxidant-sensitive post-translational modifications. Critical reviews on analytical methods using mass spectrometry and other methodologies are also beneficial. When an excess of reactive species or endogenous reduction of antioxidant defense system occurs, proteins, lipids, DNA and other macromolecular complexes are targeted to be oxidative modifications. An accumulation of altered forms of nucleic acids, lipids, and proteins damages cellular and tissue func-

