Preface

The "omic" revolution has spurred a variety of investigative techniques in a host of model systems. One of the many fields of biomedical inquiry that has benefited from the proliferation of high-throughput molecular screening methods has been the field of surrogate tissue analysis. The combination of "omic" technologies with surrogate tissue analysis has led to a rapid increase in the amount of data concerning levels of transcripts, proteins, metabolites, and other molecules present in surrogate tissues. Concomitant with this exponential increase in knowledge has been the simultaneous need to understand the relevance of these observations, and how they may be put to beneficial use.

Surrogate tissue analysis refers in general to the assessment of nontarget or off-target tissues in the body for biochemical, molecular, or cellular correlates or indicators. At its core, surrogate tissue analysis can lead to the identification of bona fide biomarkers with applications in drug discovery and development, toxicity and risk assessment, and even clinical patient management. The main attraction of surrogate tissue analysis lies in its obvious accessibility — the sampling of cerebral spinal fluid (CSF) to determine the effectiveness of a drug inhibiting neurodegeneration is eminently more feasible than the harvesting of a brain biopsy for the same purpose. Thus, it is in this manner that understanding molecular and cellular events in surrogate tissues in the context of disease, therapeutic intervention, and toxic exposure may ultimately provide the greatest benefit.

The present textbook, *Surrogate Tissue Analysis: Genomic, Proteomic, and Metabolomic Approaches*, represents a collection of chapters describing initial applications and considerations for "omic" technologies in the field of surrogate tissue analysis. The introductory chapter sets the stage for this field of inquiry and highlights some of the important issues to consider prior to conducting profiling studies in surrogate tissues. The next three sections of the textbook review specific advances in the field of genomic, proteomic, and metabolomic approaches in surrogate tissues.

In the first of these three sections, transcriptional profiling approaches in surrogate tissues are covered, and the preponderance of chapters focused on peripheral blood profiling provides hardy evidence that this field is rapidly spawning its own subspecialty — that of hemogenomics. Chapter 2 reviews the important considerations in peripheral blood profiling in great detail and summarizes results achieved when evaluations of various blood preparation platforms are used for the purpose of transcriptional profiling. Chapters 3 and 4 cover the relatively novel application of transcriptional profiling in neurological and oncological disease settings, respectively. Chapter 5 reviews the nature of surrogate tissue profiles of toxic exposure in preclinical studies where transcriptional effects in both target and surrogate tissues can be compared. Finally, Chapter 6 focuses on transcriptional profiling in a non-blood-based tissue, semen, which is utilized as a surrogate tissue for paternal exposure.

The next section focuses on proteomic and protein-based methods for identifying markers in surrogate tissues. Chapter 7 highlights mass spectrometry approaches for assessment of proteins in serum, with a focus on the obvious implications of protein-based biomarkers for detecting and monitoring early stages of cancer. Chapter 8

assesses the ability of circulating lymphocyte integrins to indicate endometrial receptivity, and Chapter 9 demonstrates how the surrogate tissue of nipple aspirate fluid can be used to detect and monitor breast cancer in afflicted patients.

The next section explores metabolomic approaches along with other novel molecular screens that can be applied in surrogate tissues for the purpose of finding biomarkers. Metabolomics is somewhat unique in that it is particularly suited to surrogate tissue analysis, since in contrast to most DNA, RNA, and intracellular proteins in the body, only metabolites (and secreted polypeptides) are freely found in surrogate tissues. Chapters 10 and 11 therefore review the field of metabolomics and how this technology is rapidly developing into a powerful technique for biomarker identification. Chapter 12 provides an excellent overview of a subfield of metabolomics, which focuses exclusively on the measurement of lipids and is appropriately termed lipidomics, and explores how the field of lipidomics can be used in surrogate tissues to provide an understanding of dynamic inflammatory responses in hosts. Chapter 13 reviews a PCR-based approach to detect and monitor metastatic cells in the circulation, and Chapter 14 covers a methylation profiling approach that can be used to accomplish a similar end.

The final section of the textbook attempts to look toward the horizon in more general terms, with chapters that focus on regulatory, economic, and pan-omic strategies, all of which will undoubtedly influence surrogate tissue analysis in the future. Chapter 15 summarizes generally applicable regulatory issues that will undoubtedly be important considerations for those biomarkers discovered in surrogate tissue profiling studies that support drug/co-diagnostic registration and require regulatory approval. Chapter 16 provides an esoteric and interesting evaluation of the value of profiling approaches to drug development in general; these sorts of economic analyses will prove of greater and greater value as the parameters affecting the "value" of biomarkers and profiling approaches become better understood. Chapter 17 reviews current concepts in pan-omic approaches during drug development where a compendium of data generated by multiple profiling approaches is assessed and evaluated—otherwise known, at least in part, as the holy grail of systems biology.

The last chapter provides a brief survey of findings in surrogate tissues that lie outside the covers of this textbook, summarizing important studies in this young field and looking to the future as well. It also discusses the burgeoning need for well-characterized and reproducible surrogate tissue analysis approaches as the requirement for biomarkers in the field of translational medicine is realized. One of the most exciting and simultaneously difficult characteristics of interpreting results from surrogate tissue profiling experiments today lies in the fact that there is often no precedent in the literature for the findings. Why do circulating peripheral blood mononuclear cells of renal cancer patients "look" different from those of healthy individuals at the transcriptional level? Are there clues to components of diseases that have been hitherto less explored — for instance, immunological responses of peripheral circulating cells to weakly immunogenic or nonimmunogenic solid tumors — and can this new knowledge be used to identify biomarkers of disease, but possibly to exploit mechanistically relevant pathways influencing disease progression by therapeutic intervention? These types of questions along with the constant efforts and the balance of innovative thinking with careful attention to details — both biological and technical — which are currently

being exhibited by investigators in the field of surrogate tissue analysis would seem to ensure that this area of biomedical research will enjoy continued success in the years to come.