Biomarkers in
KIDNEY DISEASE

Edited by

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To My Wife Freda and Children
Craig, Jeremy and Joy

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FOREWORD

The prevention or attenuation of the severity of disease necessitates early detection. In recent years this has been a focus relative to kidney disease. **Biomarkers in Kidney Disease** edited by Charles Edelstein summarizes advances in early detection and assessment of severity in an array of important kidney diseases. State of the art techniques, including metabolomics and proteomics, are discussed in areas of acute kidney injury, kidney transplantation, renal cancer, diabetic nephropathy and other glomerular diseases, as well as in preeclampsia.

Biomarkers in Kidney Disease is a seminal book, because nephrology has lagged behind other subspecialties in performing interventional trials which can improve the lives of their patients. A major reason is because the tools to detect kidney disease at the early stage have heretofore not been available. As in all diseases, prevention and attenuation of severity necessitates early intervention. The emergence of sensitive biomarkers of early kidney disease now has the potential to allow early detection and intervention. With this book there is now a source which provides up to date and important information by distinguished authors about biomarkers available to detect early kidney disease.

Louis Pasteur stated, "Science knows no country, because knowledge belongs to humanity and is the torch which illuminates the world." Charles Edelstein and colleagues have illuminated the emerging field of early detection in **Biomarkers of Kidney Disease**.

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PREFACE

The importance of developing and defining biomarkers of kidney diseases that can be used for early diagnosis, assessment of severity, and long term prognosis has been emphasized by the American Society of Nephrology and the National Institutes of Diabetes, Digestive and Kidney Diseases (NIDDK). Over the last ten years, there has been exponential growth in research on biomarkers of kidney diseases. Preclinical studies have been taken to the bedside and it is now possible to use biomarkers to diagnose certain kidney diseases at an earlier stage than has been possible with conventional tests. This prospect of early diagnosis and treatment of kidney diseases has made biomarker research one of the most exciting areas of kidney research.

Biomarkers of Kidney Disease offers a thorough examination of the latest findings in the field for both the practicing physician as well as the biomedical researcher. Coverage includes biomarkers of acute kidney injury, chronic kidney disease, kidney transplant rejection, delayed kidney allograft function, renal cell cancer, glomerular disease, diabetic nephrop athy, and preeclampsia. This book is the most comprehensive reference yet published on the topic of biomarkers of kidney diseases.

Dr. Prasad Devarajan, a pioneer in taking biomarkers from the bench to the bedside, makes the case that biomarkers are the essential tools for the implementation of personalized medicine. He reviews how novel biomarkers were discovered and validated, and he systematically lays out the general characteristics of an ideal biomarker.

For the physician interpreting or planning biomarker studies, the chapter by Drs. Chirag R. Parikh and Heather Thiessen Philbrook discusses both traditional and emerging statistical methods for evaluating the classi fication performance of biomarkers.

Proteomic and metabolomic profiling of body fluids and tissues can provide a landscape of simultaneous changes in thousands of proteins and metabolites during the body's responses to diseases and drug treatments. Dr. Uwe Christians, who has state of the art laboratories at the University of Colorado for biomarker discovery using mass spectrometry, proteomics, and metabolomics, has written two comprehensive chapters on the use of metabolomics and proteomics in kidney diseases.

BUN and serum creatinine are not very sensitive and specific markers of kidney function in AKI as they are influenced by many renal and non renal factors independent of kidney function. Drs. Charles Edelstein and Sarah Faubel review the numerous biomarkers of AKI that are released by the "injured" kidney, many of which increase before serum creatinine. Dr. Alkesh Jani, a transplant nephrologist, has written the chapter on biomarkers for the early diagnosis of delayed kidney graft function or rejection.

Cystatin C was found in the urine in 1961. Twenty years later at the University of Lund in Sweden, Drs. Anders Grubb and Helga Lofberg isolated and sequenced this "mysterious" protein as part of the cystatin family of proteins. We are fortunate to have Dr. Grubb write the chapter on cystatin C as a biomarker in kidney diseases.

Novel biological therapies for renal cell cancer are being used and there is a need to identify markers that predict response to a particular agent. The current field of renal cancer biomarkers is comprehensively reviewed by Dr. Roz Banks and colleagues.

Diabetic nephropathy and glomerulonephritis are the commonest causes of ESRD in the USA. Dr. Jon Klein and colleagues review the role that proteomics has played in answering the "how, when and why" of diabetic nephropathy. Biomarkers for the early diagnosis, early prediction of flares and prediction of outcome in patients with glomerulonephritis are reviewed by Dr. John M. Arthur and colleagues.

Preeclampsia is the most common renal complication of pregnancy and is a leading cause of maternal and perinatal morbidity and mortality. Dr. Ananth Karumanchi and colleagues review their exciting work that circulating angiogenic factors like soluble Fms like tyrosine kinase 1 (sFlt 1), in addition to heralding the onset of preeclampsia, may also cause the disease.

The advances in our knowledge of biomarkers has never been greater. It is my privilege to edit a book written by distinguished authors who have contributed to the exciting advances in our knowledge of biomarkers.

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CHAPTER 1

Characteristics of an Ideal Biomarker of Kidney Diseases

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1. THE DISCOVERY OF BIOMARKERS

The quest for biomarkers is as old as medicine itself. From the earliest days of diagnostic medicine in ancient Egypt, to the misguided science of phrenology (the belief that skull measurements could predict personality traits), to the powerful discoveries of modern science, we have been search ing for measurable biological cues that will allow us insight into the physiological workings of the human organism. In its simplest definition, a biomarker is anything that can be measured to extract information about a biological state or process. The NIH Biomarkers Definitions Working Group has defined a biological marker (biomarker) as "A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.[1]"

Biomarkers appear in every form. Body temperature, in the form of a fever, can signal infection. Blood pressure and cholesterol levels can predict cardiovascular risk. Tracking biomarkers such as height and weight can give clues to normal human growth and development. Such general biomarkers have been used for decades or even centuries and have remained powerful tools for tracking general biological activity. However, the era of person alized medicine is well upon us. Ushered in by the remarkable genomic and proteomic advances in our understanding of health and disease, personalized

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