THERAPEUTIC DRUG DEVELOPMENT FOR KIDNEY DISEASES

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1 INTRODUCTION

Diseases that affect the kidney can be thought of in terms of the functional compartment that is affected by the pathogenic cause. These compartments include the renal vasculature, glomeruli, renal interstitium, renal tubules, and urinary collecting system. In each of these compartments, processes can be acute or chronic in nature and can lead to severe disease that would require some form of renal replacement therapy (hemodialysis, peritoneal dialysis, or kidney transplantation). Current therapeutic agents for kidney disease are limited and for the most part are not specifically targeted to pathogenic pathways. Given the epidemic of chronic kidney disease (CKD) (estimates are that over 8 million people in the United States have an estimated glomerular filtration rate less than 59 mL/min) [1], there is an urgent need for therapeutic agents that target this problem. Furthermore, in those patients with CKD, management of the complications associated with this disease state such as anemia and metabolic bone disease need to be effectively managed to avoid serious complications. Finally, in those patients who advance to end-stage renal disease, therapies to improve the outcomes of renal transplantation are needed.

This chapter will explore drug development across the spectrum of kidney disease. This ranges from acute kidney injury (AKI) to specific causes of chronic kidney disease such as polycystic kidney disease. Drugs to effectively manage the complications of CKD are also discussed. Finally, in each section, common obstacles to drug development for this disease state are discussed.

2 DRUG DEVELOPMENT FOR ACUTE KIDNEY INJURY

Acute kidney injury is due to a variety of conditions and has serious consequences. There are numerous definitions of AKI, but in general this term refers to the acute deterioration in renal function as manifested by rises in serum creatinine and fall in urine output. Clinically, this leads to impairment in the excretion of waste products and fluid and in the extreme the need for dialysis. Using large databases of U.S. hospitalizations over the past 10–15 years, there is evidence for a marked increase in the incidence of AKI [2, 3]. This, in part, reflects the increasing comorbidity and age of patients suffering AKI. It is widely recognized that AKI leads to high morbidity and mortality in hospitalized patients. While there may be evidence that morality rates are decreasing, [2, 3] they remain unacceptably high, and there is an urgent need for effective therapy [4].

Except for a few isolated studies, the vast majority of animal and clinical studies have yet to conclusively demonstrate the benefit of pharmacological treatment for AKI. Table 1 summarizes potential factors that have contributed to the lack of success of human studies. Table 2 describes novel pharmacological therapies on the horizon for the treatment.

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