The bioartificial kidney

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Renal failure has an exceedingly high mortality rate despite advances in dialysis technology. Current renal replacement therapies (RRTs) restore only the filtration function of the kidney. Replacing the critical transport, metabolic, and endocrine functions of the kidney may provide more complete RRT, changing the natural history of these disease processes. Primary human renal epithelial cells (RECs) have been isolated and expanded under conditions that enhance propagation, resulting in maximum cell yield for use in bioengineered applications. These RECs demonstrate differentiated absorptive, metabolic, and endocrine functions of the kidney when tested under *in vitro* and preclinical *ex vivo* animal studies. When incorporated into bioengineered systems, RECs have proved to provide effective RRTs in both preclinical and clinical studies. These engineered "bioartificial kidneys" demonstrate metabolic activity with systemic effects and improvement of survival in patients with acute kidney injury and multiorgan failure. Results also indicate REC therapy influences systemic leukocyte activation and the balance of inflammatory cytokines, suggesting that this REC therapy may improve morbidity and mortality by altering the proinflammatory state of patients. This innovative approach for treating renal and inflammatory disease states may become a groundbreaking, transformative platform to current standard-of-care therapies, enabling the advancement of numerous life-saving technologies. (Translational Research 2014;163:342–351)

Abbreviations: AKI = Acute kidney injury; BAK = Bioartificial kidney; BRECS = Bioartificial renal epithelial cell system; EP = Enhanced propagation; ESRD = End-stage renal disease; FDA = Food and Drug Administration; IL = Interleukin; IND = Investigational new drug; MOF = Multiorgan failure; PD = Peritoneal dialysis; QA = Quality assurance; QC = Quality control; RAD = Renal assist device; REC = Renal epithelial cell; RRT = Renal replacement therapy; SSMOD = Septic shock-associated multiorgan dysfunction

An evolving field in the treatment of acute and chronic disease is the area of biomedical engineering, especially in the development of bioengineered cell-based therapeutics.[1] The potential clinical impact of this therapeutic approach is based on the emerging understanding that the majority of disease processes develop as a result of interactions between complex biosystems involving numerous types of cell products, rather than the deficiency of a single protein. Cell-based therapeutics are dependent on cell and tissue culture methodologies that expand specific cells that have the ability to replace important differentiated processes deranged or lost in various disease states. Recent approaches have made progress by seeding cells into hollow fiber bioreactors or encapsulating membranes as a means to deliver cell activities to a patient.[2,3] A natural extension of this approach, in the area of renal replacement therapy (RRT), would

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be the addition of renal cell-based therapeutics to the current renal substitution processes of hemodialysis, hemofiltration, and peritoneal dialysis (PD).[4-6] Acute hemodialysis or hemofiltration has yet to reduce the mortality rate of acute kidney injury (AKI) to less than 50%, despite advances in synthetic materials and extracorporeal circuits.[5,6] Consequently, AKI may be especially amenable to cell therapy in conjunction with continuous hemofiltration techniques, particularly because AKI develops predominantly as a result of injury and necrosis of renal proximal tubule cells. Early replacement of the functions of these cells during an episode of AKI, in conjunction with the current standard of care of hemodialysis, could potentially provide near-complete RRT.

In addition to renal cell-based therapy providing therapeutic efficacy for renal indications, both preclinical large-animal study results[7-11] and clinical trial outcomes[12-14] have indicated this cell-based therapy may play an important immunoregulatory role in the treatment of septic shock. With respect to this, death in patients with AKI is frequently preempted by the onset of systemic inflammatory response syndrome, most often secondary to sepsis, resulting in cardiovascular collapse, ischemic damage to vital organs, and multiorgan failure (MOF).[15-17] The predisposition of patients with AKI to develop systemic inflammatory response syndrome and sepsis suggests that renal function, specifically renal tubule cell function, plays a critical immunomodulatory role in individuals under clinically stressed disease states.

To appreciate more fully the vast potential of renal cell-based therapy, one needs first to understand the role of the renal tubule epithelial cell in, not only the well-accepted processes of renal metabolism, but also a less recognized function of the kidney and the renal tubule cell: immunoregulation of systemic inflammatory responses. During development, the kidney is derived embryologically from dorsal mesoderm, a collection of cells also essential in the development of bone marrow stem cells.[18,19] Of note, the maturation of cells responsible for erythropoietin synthesis and activation of 1,25-dihydroxyvitamin D_3 in the kidney is reflective of this embryonic origin. Phylogenetically, in bony fish and amphibians without lymph systems, the kidney is the major antibody-producing organ.[20,21] Predicatively, as part of the evolutionary process, mammalian renal proximal tubule cells are active immunologically. They are antigen-presenting cells[22-24] that have costimulatory molecules[25] and synthesize and process a variety of pro- and anti-inflammatory cytokines.[26-30] In support of this, patients with end-stage renal disease (ESRD) are typically in a chronic proinflammatory state, indicative of a reduction in immunologic function.[31-33] The degree of inflammation in patients with ESRD has been shown to be highly correlated with mortality rates.[32-36] Diminished renal tubular cell metabolic function, rather than reduced renal filtration and clearance, may very well be the cause of the inflammatory dysregulation observed in these patients. These factors, taken into consideration collectively, are the foundation for the development of the bioartificial kidney (BAK).

This review article details the development, to date, of the BAK, the regulatory and manufacturing challenges encountered during this development process, solutions to these challenges, and future expectations for this exciting, emerging field of bioengineered RRT. In addition to the BAK, there are various other regenerative medicine approaches for the treatment of renal disease indications. A stem cell-based therapeutic intervention has been recently assessed during a phase I clinical trial targeting patients undergoing cardiac surgery who were at high risk for AKI.[37] Preliminary findings from this phase I trial demonstrated allogeneic mesenchymal stem cell therapy to be delivered safely to patients, in addition to showing protection of renal function and reduced hospital bed days. For more detailed summaries of other stem cell approaches to treat kidney disease, and progress of nanotechnology approaches for implantable tissue-engineered RRT, there are several excellent and comprehensive reviews on these topics.[38-41]

DEVELOPMENT OF A BIOARTIFICIAL KIDNEY

The kidney is unique in that it was the first organ for which long-term *ex vivo* replacement therapy was established, with lifesaving outcomes. Renal failure before the inception of hemodialysis and transplantation resulted in certain death, and this dismal outcome of renal failure is still common outside the industrialized world. Even under optimal current RRT, mortality rates in patients presenting with AKI and MOF can be as high as 80%.[42,43] As a result of the prevalence of AKI in hospitalized patients, and this very poor clinical prognosis, recent focus has been directed toward alternate or adjunct RRTs. One of these focused efforts has been to develop a BAK to replace the functions of the renal tubule cell that are diminished during AKI.

Renal assist device. The first and, to date, only BAK that has been tested in a Food and Drug Administration (FDA)-approved clinical trial—the renal assist device (RAD)—consisted of an extracorporeal system that used a standard hemofiltration cartridge seeded with up to 10^8 renal tubule cells grown as monolayers along the inner surface of the hemofiltration cartridge hollow