and negative regulatory mechanisms intact. It is important to note that EPO-deficient anemias, while prevalent in patients with kidney disease, can also develop as a result of other disease states, including heart failure, multi-organ system failure, and other chronic diseases.

[0007] The kidney is a unique organ comprised of many different specialized cell types (>10), all of which originate developmentally from the intermediate mesoderm but at maturity form morphologically and functionally distinct compartments, and anatomical units that act in concert to provide filtration of the blood, production of urine, regulation of acid-base and electrolyte balance, and regulated endocrine functions such as the production of erythropoietin (Epo), Vitamin D, renin, and angiotensin. The cellular compartments of the kidney are heavily interdependent for homeostatic function, as highlighted by the following examples. Cells of the afferent arterioles act in concert with specialized tubular cells in the thick ascending limb of the loop of Henle (Macula Densa) to regulate blood flow through the glomerulus (Castrop, H. Acta Physiol (Oxf), 189: 3-14, 2007). Protein handling by the kidney is orchestrated by the fenestrated endothelial cells, podocytes, and basement membrane of the glomerulus paired with the receptor-mediated endocytosis and resorption of protein from the glomerular filtrate by specialized proximal tubular cells (Jarad, G & Miner, J H. Curr Opin Nephrol Hypertens, 18: 226-32, 2009). Production of active vitamin D by tubular cells regulates homeostasis of interstitial cells through direct and indirect mechanisms that control extracellular matrix deposition, conversion of interstitial cells to myofibroblasts, and epithelial-mesenchymal transformation (Tan, X, et al. J Steroid Biochem Mol Biol, 103: 491-6, 2007). Regardless of the specific example, all cell-cell interactions in the kidney are at least partially dependent on spatial and architectural relationships. At the cellular level, progression of CKD may involve loss of a particular cell type or loss of function of one or more cell types due to cellular insufficiencies or loss of homeostatic cell-cell interactions. Thus, successful regenerative approaches to the treatment of CKD must re-establish homeostasis in part through restoration of cellular organization and intercellular communication.

[0008] Augmentation of specific kidney functions, such as tubular transport or production of Epo, has been contemplated with the intention of reducing the morbidity and mortality associated with progression of CKD. The majority of cell-based treatment approaches for kidney disease have focused on therapeutic intervention of acute renal failure (ARF) with stem or progenitor cell types (Hopkins, C, et al. J Pathol, 217: 265-81, 2009). There have been many preclinical studies involving the delivery of various cell types immediately before or after induction of ARF, including intrarenal or systemic delivery of MSCs (Humphreys BD & Bonventre J V, Annu Rev Med 2008, 59:311-325), endothelial progenitors (EPCs) (Chade A R, et al., Circulation 2009, 119:547-557, Patschan D, et al., Curr Opin Pharmacol 2006, 6:176-183), and fetal cells or tissue rudiments (Hammerman M R, Curr Opin Nephrol Hypertens 2001, 10:13-17; Kim S S, et al, Stem Cells 2007, 25:1393-1401; Marshall D, et al., Exp Physiol 2007, 92:263-271; Yokoo T, et al., J Am Soc Nephrol 2006, 17:1026-1034). An extracorporeal hollow-fiber filtration device containing renal tubular cells was tested as an adjunct to traditional dialysis for the treatment of ARF in humans (Ding, F & Humes, HD. Nephron Exp Nephrol, 109: el 18-22, 2008, Humes, H D, et al. Kidney Int, 66: 1578-88, 2004, Humes, H D, et al. Nat Biotechnol, 17: 451-5, 1999). Transplantation of mesenchymal stem cells via the renal artery is also being tested clinically in a population of patients at high risk for an ARF episode secondary to cardiovascular surgical procedures (Westenfelder, C. Experimental Biology. New Orleans, La., 2009). Limited preclinical studies have been conducted that address cell-based therapeutic intervention of CKD (Chade, A R, et al. Circulation, 119: 547-57, 2009, Eliopoulos, N, et al. J Am Soc Nephrol, 17: 1576-84, 2006, Kucic, T, et al. Am J Physiol Renal Physiol, 295: F488-96, 2008). The combination of fetal kidney rudiments+/−mesenchymal stem cells has been investigated in rodents (Yokoo, T, et al. Transplantation, 85: 1654-8, 2008, Yokoo, T, et al. J Am Soc Nephrol, 17: 1026-34, 2006), where it is clear that whole fetal kidney tissue transplanted to an appropriate environment, such as the omentum, can develop into kidney structures with limited function. However, the therapeutic role of the MSCs as a component of the fetal tissue rudiment is unclear, and sourcing of human fetal kidney tissue for therapeutic purposes poses many operational and ethical challenges. In other studies, cells derived from healthy donor bone marrow were transplanted into irradiated COL4A3 (−/−) mice, a model of Alport Syndrome with glomerulonephritis, protein loss, and fibrosis, where they partially slowed progression in the model via replacement of leaky glomerular podocytes with healthy cells lacking the collagen gene mutations (Prodromidi, E I, et al. Stem Cells, 24: 2448-55, 2006, Sugimoto, H, et al. Proc Natl Acad Sci USA, 103: 7321-6, 2006). Cell transplantation was credited with stabilization of sCREAT, BUN, and sodium levels, but untreated/kidney-damaged controls were not presented for comparison in the studies24. Chade et at employed a swine model of unilateral renal artery stenosis to examine the effects of autologous EPCs, delivered intrarenally 6 weeks post-injury (Chade A R, et al., Circulation 2009, 119:547-557). The EPCs improved tubulo-interstitial fibrosis somewhat, significantly improved glomerulosclerosis, and improved renal blood flow, although no change in blood pressure was observed with treatment (Chade A R, et al., Circulation 2009, 119:547-557). To date, studies that examined the in vivo efficacy of cell-based therapies for CKD have yielded transient and/or partial effects, and few studies have collected both systemic and histologic evidence of function. The limited number of studies that provide evidence of clinically-relevant benefits after intervention in progressive models of CKD raises questions about the potential of cell-based therapies to restore renal function completely. However, regenerative therapies that stabilize renal function and delay progression can address an unmet medical need within this patient population.

[0009] Reproducible in vivo model(s) of progressive CKD are essential for assessment of the therapeutic potential of candidate treatments. While models of ARF are numerous and include a variety of chemical- or ischemia/reperfusion-induced tubular injuries, there are fewer models of CKD that are progressive and terminal without significant intervention. The two-step 5/6 nephrectomy procedure in rats reproducibly generates a terminal and progressive state of renal failure, resulting in systemically- and histologically-detectable disease complete with several key features of CKD, including hypertension, reduced glomerular filtration rate (GFR), elevated serum creatinine (sCREAT) and BUN, glomerular and tubulo-interstitial fibrosis, hyperlipidemia, hyperphosphatemia, and anemia (Kaufman, J M, et al. Kidney Int, 6: 10-7, 197422, Platt, R, et al. Clin Sci (Loud), 11: 217-31,