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Grant Title: Identification of Kidney Regeneration Mechanisms Using the Zebrafish

Grant Body Abstract:

Kidney diseases occur at epidemic proportions worldwide. Common among kidney disease pathology is the destruction of cells that comprise the nephron, the basic structural and functional unit of the kidney organ. Interestingly, human nephrons have the capacity to replace damaged nephron cells through regeneration. However, this observation is at odds with the growing incidence of acute and chronic kidney diseases: while nephrons exhibit regenerative capacity, there are striking, unknown limits to this property. Currently, the mechanisms that are responsible for driving nephron regeneration are a mystery. Patients with kidney disease are compelled to undergo dialysis regimens while awaiting organ transplant, often waiting several years before an organ is available, and the situation is steadily becoming more dire as kidney disease rates elevate in tandem with the rise in obesity-related diabetes and extensions in human lifespan.

An innovative approach to discovering alternative kidney disease treatments is to discover the molecular signals that can instruct nephron regeneration using a patient's existing kidney cells as the regeneration source. I have created an original model of nephron regeneration in zebrafish, and propose to use this zebrafish model in my laboratory to uncover the mechanisms that direct nephron regeneration. I previously demonstrated that nephrons are similar in zebrafish and humans, suggesting that mechanisms of nephron regeneration are likely to be conserved. We will utilize the attributes of the zebrafish to discover the pathways that can modulate nephron regeneration in vertebrates, taking advantage of the ability to visualize and record cellular events in real time and perturb molecular events with high resolution using transgenics, gene knockdown and mis-expression tools. Our zebrafish kidney regeneration model provides an unprecedented, new opportunity to visualize nephron cell regeneration and conduct experimental studies in the context of a whole vertebrate animal. To date, the study of nephron regeneration has been virtually impossible to address at the level of molecular genetics with existint mammalian kidney disease or injury models. The proposed studies will (1) delineate the cellular and molecular events involved in nephron regeneration, and (2) elucidate the signaling pathways that are able to induce, enhance, or obviate regeneration. Our findings will delineate a paradigm of nephron regeneration that may lead to novel therapeutics that enable the restoration of kidney function in various disease states.

Lay Narrative:

Diseases of the kidney are widespread and cause damage to nephrons, the functional units that cleanse the body of waste and regulate water balance. Nephron damage cannot be restored with current medical treatments. The proposed studies will determine how nephron cells can be regenerated following damage, and understanding this process has the potential to guide generation of novel therapies for kidney disease.