Dr. Jonathan Barasch

The critical function of the kidney, conserved from planaria to mammals, is to regulate the extracellular fluid volume. When Na and water are scarce and volume decreases, the kidney's excretory function also decreases, ensuring the conservation of Na and water but also retaining waste products such as serum creatinine (sCr). Unfortunately, the same homeostatic pathways that regulate effectors of volume retention are appropriated by diseases such as heart failure and cirrhosis even in the absence of volume depletion. Adding further complexity, direct damage to the epithelia of the nephron, such as ischemia and bacterial endotoxins also decrease the kidney's excretory function and raise sCr. Hence while the two metrics of kidney function, a rise in sCr and a decrease in urine output are considered tantamount to kidney epithelial injury, neither criterion emphasizes the heterogeneity of kidney failure. Our ignorance of patient specific diagnoses results in daily misdiagnoses and mistreatments.

We identified a kidney injury protein that serves a novel antimicrobial/iron chelation function in the urinary tract. NGAL/Lcn2 is not expressed at baseline, but ischemia and a few other injuries induce transcription 1000 fold in 3-6 hours. Most exciting (i) NGAL was induced only in the setting of authenticated tubular damage and (ii) NGAL originated from specialized collecting duct cells. These data suggested that different cells respond to different extrarenal stimuli. Methods, such as in situ RNA pulse-chase techniques have confirmed that even neighboring cells have different responses to stresses.

The tools that can change our paradigms and provide molecular diagnoses are under development at Columbia, and in this pilot we request funds to begin the process by documenting the transcriptome of normal human kidneys. We have studied many technical approaches, but the most reliable data results from capitalizing on anatomical and spatial differences in kidney segments. We propose to create a map of the normal kidney by microdissecting human nephrons with advanced training in M. Knepper's lab (NIH), and then analyzing each segment by using a single nuclear approach with the molecular tools invented by Sims (Columbia) and statistical tools developed by Rabadan and Kiryluk (Columbia).

The choice of these tools is based on the following: the nephron is composed of many segments, and each is likely to express genes in a gradient along a cortical medullary axis. In addition, some cells of the nephron are known to undergo conversion to a second cell type. Consequently, a cell by cell approach tied to the basic segmental architecture of the nephron will yield interpretable data. The second reason for our approach is that the map will be a critical reference to interpret data from kidney biopsies of patients with acute injury (discussed in in upcoming NIH submissions). Biopsies contain small numbers of cells with disorganized architecture and hence a change in gene expression can only be understood if mapped to normal segments and their different cell types. Taken together, we expect to find anatomically-etiologically specific molecules which we will test in patient specific diagnoses.

We have assembled a team of scientists from Nephrology-Medicine, Urology, Systems Biology, and experts in NephroPathology and help from NIH scientists and each member of the Columbia team is committed to the upcoming program grants and RO1 submissions for Precision Medicine. Preliminary data indicate that our plans from tissue procurement to cell harvest to statistical interpretation are feasible and within budget.