Bradley K. Yoder, PhD
Heersink School of Medicine, University of Alabama at Birmingham
Professor / Chairperson, Cell, Developmental, and Integrative Biology

Talk Title: **Cilia, Injury, and Cystic Kidney Disease.**

**Abstract:**
Disruption of cilia (*Ift88* mutants) or cilia function (*Pkd1/Pkd2* mutants) in mice results in cyst formation in the kidney. In humans, most cases of PKD are caused by mutations in PKD1 or PKD2. *Pkd1* and *Pkd2* encode the polycystin 1 and 2 proteins that form a cilia localized channel complex. Despite the polycystins localizing and presumably functioning in the cilium, the cystic phenotype in *Pkd1* or *Pkd2* mutants is always markedly more severe than that observed in the *Ift88* mutants. Surprisingly, when *Ift88;Pkd2* double mutants were analyzed, they were found to have a mild cystic phenotype resembling that of the *Ift88* single mutant. The mechanism involved in the epistatic relationship between the polycystins and the cilium is not understood. In previous studies, we and others demonstrated the time at which cilia dysfunction occurs is important for cyst severity. Disrupting *Ift88* or *Pkd1/Pkd2* in juvenile mice (~less than 14 days old) causes rapid and severe cyst formation involving nearly all nephrons. However, when these mutations are induced in adult mice (post 14 days) cyst formation occurs slowly over several months. Additionally, the cysts that form in the adult induced mutants occur in focal areas, initially affecting relatively few nephrons. This is despite nearly all epithelial cells in the kidney being mutant for these genes. These data suggest a stimulus in addition to cilia dysfunction or loss is needed for cyst initiation. A possible hint as to a potential mechanism was identified when renal injury (e.g., ischemia reperfusion, cisplatin) was found to accelerate cystogenesis and cyst severity in adult induced *Ift88* or *Pkd2* mutants. Further, the cysts that form after injury now occur throughout the kidney, in contrast to the focal nature observed in non-injured, aged mutants. Based on these data, we propose that one possible function of the cilium and PKD1/PKD2 complex in the cilium is to regulate injury and repair responses. Thus, cysts may arise from the expansion of an injured epithelium that is unable to properly regulate and execute this repair process. Our analysis of the *Ift88*, *Pkd2,* and *Ift88*;*Pkd2* double mutants indicate there are changes in the inflammatory response involving increased cytokine production, altered expression of injury markers, along with an increase in accumulation of innate immune cells, particularly resident macrophages, that directly correlate with the severity of the cysts that will form in each genetic background. These resident macrophages align along the early cysts where they are highly proliferative suggesting paracrine signals between the epithelium and the macrophage. Our analysis in human PKD patients similarly identified resident macrophage accumulation around the cyst suggesting a conserved mechanism. To explore a possible role for macrophages in the cystic phenotype, we impaired resident macrophage accumulation genetically and through pharmacological approaches. In both the adult induced injured and non-injured mutants, preventing resident macrophage accumulation attenuated cyst formation. In contrast, there was no overt effect on cyst formation when this was done in the juvenile induced models. In summary, our data indicate that cyst formation in juvenile and adult induced mutants may occur through different processes and support a model wherein PKD1/PKD2 regulate

activation and repression of a pathway requiring the presence of the cilium that is involved in injury and repair.