et al., 1998). We show that BMP7 signaling in the cloacal endoderm and the urorectal mesenchyme is mediated by the non-canonical WNT/planar cell polarity (PCP) pathway. Loss of Bmp7 results in disruption of the membrane PCP complexes, containing VANGL2, and in a significant decrease in the activity of the Rho, JNK and c-Jun kinases, the downstream mediators of the PCP pathway. We further show that knockout of Bmp7 results in disruption of the apical–basal polarity in the cloacal endoderm, a delay in epithelial differentiation, decreased survival, and defects in cell adhesion in the septum area. Based on our data, we propose that BMP7 signaling from the urorectal mesenchyme directs dorsal–ventral partitioning of the cloaca by collaborating with PCP pathway, and by directing cell fate choice of the epithelial progenitors in the septum area.

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Program/Abstract # 116
A role for planar cell polarity during kidney tubule morphogenesis
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Failure of proper kidney tubule development can result in polycystic kidney disease (PKD), one of the most common genetic disorders inherited in humans. With no available cure, more than half of the patients with PKD develop kidney failure. Genetic analysis has revealed that many of the causative gene products identified from patients with PKD localize to or interact with components of the primary cilium, but how they regulate kidney tubule morphogenesis is unclear. Recent research suggests that kidney tubule morphogenesis may involve convergent extension movements and oriented cell division, two processes that require input from the planar cell polarity (PCP) pathway. However, the interconnectivity between components within the primary cilium, the PCP pathway, and the developmental processes that regulate kidney tubule morphogenesis is tenuous. We present results that demonstrate a definitive role for BMP4 and its downstream mediator, PCP, in the development of kidney tubule morphogenesis.

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Program/Abstract # 117
The BMP co-receptor Dragon is required for normal renal branching morphogenesis
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Reductions in branching morphogenesis and nephrogenesis (renal hypoplasia/dysplasia) can result in renal failure or adult-onset hypertension. The cellular and molecular mechanisms involved are not fully understood. Normal kidney development is dependent on mesenchymal–epithelial interactions in embryonic kidneys. Evidence suggests that bone morphogenetic protein (BMP) signaling is critically involved in the reciprocal inductive interactions between mesenchymal and epithelial cells. Kidneys of BMP4 null heterozygote mice showed slower growth and branching of ureteric buds. BMP4 is expressed in the mesenchyme adjacent to the bodies of ureteric branches. BMP4 normally utilizes BMPRII rather than ActRIIA for signaling. Interestingly, ActRIIA but not BMPRII is the predominant BMP type II receptor found in the bodies of ureteric branches, thus raising the question as to how BMP4 from the mesenchyme can efficiently signal in ureteric branch cells. Recently we have found that Dragon (also known as RGMb), a GPI-anchored protein, functions as a BMP co-receptor that allows BMP4 to signal via ActRIIA. Our results show that Dragon is highly expressed in the epithelial cells of ureteric branches in the embryonic kidney. Dragon overexpression increased tubule formation and branching in IMCD3 cells in 3D culture. Kidneys from Dragon null mouse fetuses at E13.5 showed significant reduced ureteric branching compared to the wild type. These results suggest that Dragon promotes tubulogenesis in vitro and renal branching morphogenesis in vivo.

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Program/Abstract # 118
Identifying genes involved in ureteric bud morphogenesis
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The ureteric bud (UB) emerges from a swelling of the caudal Wolffian duct (WD) at –E10.5 of mouse development. This swelling develops as a result of Ret-dependent cell movements and is termed the “primary UB tip domain”. Correct UB outgrowth is essential for further kidney development; renal agenesis occurs when the UB fails to emerge — as seen in mice homozygous for loss of Ret. To identify genes that might mediate Ret-dependent UB outgrowth we screened for genes that are differentially expressed between rostral and caudal WD, and those whose expression depends on Ret. Microarray analysis of E10.5 wild type rostral WD, wild type caudal WD, and Ret−/− caudal WD revealed genes with differential expression. Several genes with known roles in UB development were confirmed to be upregulated in the caudal WD, as were a number of genes with known roles in cell movement and associated processes, but not known to be involved in kidney development. We examined expression of these candidate genes using in situ hybridization and transgenic reporter lines, and confirmed novel UB expression for a number of the candidates. Cxcr4, encoding a receptor for the chemokine CXCL12 which is implicated in cell migration and transgenic reporter lines, and confirmed novel UB expression for a number of the candidates. Cxcr4, encoding a receptor for the chemokine CXCL12 which is implicated in cell migration, was upregulated in the caudal WD. Previous work in our lab suggests a role for this gene in UB morphogenesis downstream of Ret. We therefore investigated whether Cxcr4−/− cells can contribute to the UB in Cxcr4−/− wild type chimaeric embryos. Cxcr4-deficient cells could populate all parts of a morphologically normal UB, including the tips, indicating that Cxcr4 is not required for UB development. We are now investigating the interplay between Cxcr4, Cxcr7 (a related chemokine receptor), and Cxcl12 in kidney development.