

## **SPROUTY1 AND GDNF/RET SIGNALLING IN KIDNEY DEVELOPMENT.**

Odyssé Michos<sup>1</sup>, Debbie Hyink<sup>2</sup>, Jon Licht<sup>3</sup>, and Frank Costantini<sup>1</sup>

1. Columbia University Med. Center, New York, NY. 2. Mount Sinai School Of Medicine, New York, NY. 3. Northwestern Univ. Feinberg School of Medicine, Chicago, IL.

The development of the metanephric kidney begins when the Wolffian duct, an epithelial tube derived from intermediate mesoderm, gives rise to an out-pocketing called the ureteric bud (UB). The UB then undergoes a complex process of growth, branching and remodelling, to eventually give rise to the entire urinary collecting system. Signalling by GDNF through its receptor tyrosine kinase (RTK) Ret is required for normal growth of the ureteric bud during kidney development. However, the precise role of GDNF/Ret signalling in renal branching morphogenesis and the specific responses of UB cells to GDNF remain unclear. Recent studies have shown that Sprouty1 (Spry1), an intercellular RTK antagonist, was an important regulator of GDNF/Ret signalling. However, it is still not clear whether or not Spry1 only regulates GDNF signalling and especially how it acts? To gain insight into the mechanism of action of Spry1 we have now, generated chimeras by injecting Spry1<sup>-/-</sup> ES cells into wild type blastocysts. Our data show that Spry1<sup>-/-</sup> UB cells preferentially contribute to the tips of the developing UB. These observations support the model that Spry1 opposes GDNF/Ret signalling, and also suggest that Spry1 acts in a cell-autonomous manner. Interestingly, we have generated double mutant animal lacking both Spry1 and Gdnf and found that such mutant develop fairly normal kidneys. Moreover, we also found that FGF10 is an important factor necessary to promote kidney development in absence of GDNF and Spry1. These results suggested that several RTK signals are required for proper branching morphogenesis and kidney development.