Deletion of *Ift27* in an adult ADPKD mouse model does not reduce disease severity

Aakriti Chaturvedi;[1, 2] Henry H Wang, BS;[1, 2] Matthew A Kavanaugh, BS;[1, 2] Dona G Isai, PhD; [1, 2] Pamela V Tran, PhD;[1, 2]
[1]*Department of Cell Biology and Physiology; Jared Grantham Kidney Institute, University of Kansas Medical Center, Kansas City, KS*

Introduction: Remarkably, deletion of ciliary genes in adult ADPKD mouse models markedly attenuates disease severity. These ciliary genes have included *Kif3a*, a component of the anterograde intraflagellar transport (IFT) motor; *Ift20* and *Ift88,* components of the IFT-B complex; *Ttc21b*, a component of the IFT-A peripheral complex; and *Tulp3,* an IFT-A adaptor. Here we examine the role of deletion of *Ift27* or of *Ift140* in adult ADPKD mouse models. IFT27 is a member of the IFT-B core 1 complex, binds to IFT25 and works with the BBSome to shuttle signaling molecules out of the cilium. IFT140 is a component of the IFT-A core complex. Mutations in *IFT140* have been identified in ADPKD patients, who do not have mutations in *PKD1* nor *PKD2*.

Methods: Using the *ROSA26-Cre^{ERT}* in mice, *Pkd1* was globally deleted, alone or together with *Ift27*, at 5 weeks of age. Similarly, *Pkd2* was deleted globally, alone or together with *Ift140*, at 4 weeks of age. Kidneys of single and double knockout mice were analyzed at 6 months of age. Immunofluorescence was used to assess primary cilia, cell proliferation and inflammation.

Results: Deletion of *Ift27* together with *Pkd1* in adult mice did not affect ADPKD severity. Preliminary data indicate similar renal cystic indices, primary cilia lengths, cell proliferation and inflammation between *Pkd1* cko and *Pkd1;Ift27* double ko mice. In contrast, deletion of *Ift140* together with *Pkd2* in adult mice resulted in a kidney phenotype similar to wild-type mice.

Conclusion: Deletion of *Ift140* in adult ADPKD mice acts similarly to all previously reported IFT genes in mitigating disease severity. In contrast, *Ift27* is the first IFT gene identified to our knowledge that when deleted, does not counter adult kidney cystogenic processes. Elucidating the individual and unique roles of IFT proteins is essential to understanding these contrasting effects.