# Analyzing the effect of Notch inhibition on the progression of Polycystic Kidney Disease

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INTRODUCTION

Signaling pathways activated by loss of function mutation in polycystic kidney disease (PKD) constitute important targets of therapy for PKD. We have recently shown an activation of the Notch3 pathway in PKD. The expression of Notch 3 correlated with cell proliferation in the renal cystic epithelium.

METHODS

To determine the *in vivo* effect of Notch inhibition in PKD, we selected two repurposed drugs Quinomycin A (Quin) and Ciclopirox-olamine (CPX) both of which have been shown recently to inhibit the Notch pathway and ameliorate progression of cancer. First, we tested the *in vitro* efficacy of these drugs. We then intraperitoneally injected CPX (10mg/kg body weight), or vehicle, in 21 day old mice. Quin (10μg/kg body weight) was injected similarly. Studies consisted of 6 male and 6 female mice in each of the four groups: WT-vehicle, WT-drug, $PKD1^{RC/RC}/PKD2^{+/-}$-vehicle and $PKD1^{RC/RC}/PKD2^{+/-}$-drug. Mice were euthanized after 27 days of treatment. Kidneys and blood were harvested for further studies.

RESULTS

A concentration of 0.2μM CPX was found safe for ADPKD cells in culture. CPX was able to reduce the size of ADPKD cysts grown in 3D collagen gels. Treatment of PKD mice with CPX or Quin for 27 days both resulted in a significant reduction in PKD progression. Normal mice were not affected by either of these drugs. Histological analysis revealed a significant decrease in the percent cystic index. Blood urea nitrogen levels showed a decreasing trend with CPX and Quin treatment. Both treatments were associated with decreased cell proliferation of the cyst lining epithelial cells.

CONCLUSIONS

Both CPX and Quin have been shown to target Notch signaling. Further studies will be required to determine the exact mechanisms by which they confer protection in PKD. Nevertheless Ciclopirox-olamine and Quinomycin A may constitute alternate drugs of choice for PKD in the clinic.