MONASH University

Novel Targets for Polycystic Kidney Disease

THERAPEUTIC: Orphan Disease

Product Type	Small molecule
Indication	Polycystic Kidney Disease (PKD) including Autosomal Dominant Polycystic Kidney Disease (ADPKD) and Joubert Syndrome (JS).
Target / MoA	Factors A and B cross-regulate each other, driving a self-reinforcing cystogenic pathway. Eliminating Factor A or inhibiting Factor B can disrupt this process and reduce renal cystogenesis.
Development Stage	Lead series
Brief Description & Differentiation	Eliminating Factor A leads to lower Factor B activity, resulting in significantly reduced renal cystogenesis. The inventors have: • Demonstrated genetic deletion of Factor A can rescue PKD in both ADPKD and JS models. • Ruled out an existing chemical inhibitor to Factor A as a PKD drug candidate since it worsens PKD. • Identified an inhibitor to Factor B that can successfully reduce cyst burden and size in both ADPKD & JS models.
Research Team	Prof Ian Smyth
Intellectual Property	Provisional patent application filed covering methods of treating or preventing Polycystic Kidney Disease.

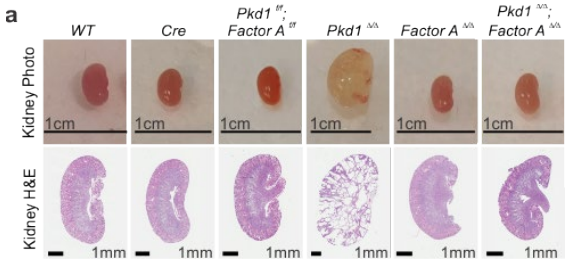

Figure 1: Co-deletion of *Factor A* rescues *Pkd1*$^{\Delta/\Delta}$-dependent cystogenesis. Representative images of mouse kidneys from indicated genotypes. Note scale difference for *Pkd1*$^{\Delta/\Delta}$ due to enlarged cystic state, while *Pkd1*$^{\Delta/\Delta}$;*Factor A*$^{\Delta/\Delta}$ mice exhibit few cysts.

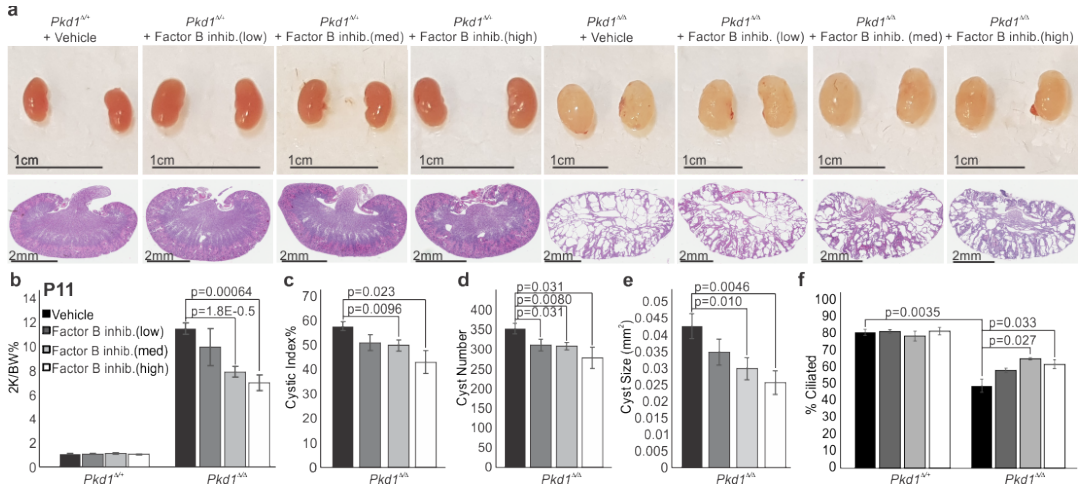

Figure 2: Inhibition of Factor B recues PKD

a. Representative images of murine kidneys following oral treatment with vehicle or Factor B inhibitor. Note smaller kidney and altered cystic appearance from Factor B inhibitor-treated *Pkd1*$^{\Delta/\Delta}$ mice relative to vehicle-treated *Pkd1*$^{\Delta/\Delta}$ mice.

b-f. Quantification of the combined kidney weight over total body weight percentage (2K/BW%), cystic index %, average cyst number per section, average cyst cross-sectional size and ciliation % for vehicle and Factor B inhibitor treated mice. Results show the Factor B inhibitor dose dependently reduces the 2K/BW%, cystic index%, number and size of *Pkd1*$^{\Delta/\Delta}$ kidneys, while increasing ciliation.