Autosomal dominant polycystic kidney disease (ADPKD) is a life-threatening monogenic disease caused by mutations in PKD1 and PKD2 that encode polycystin 1 (PC1) and polycystin 2 (PC2). PC1/2 localize to cilia of renal epithelial cells, and their function is believed to embody an inhibitory activity that suppresses the cilia-dependent cyst activation (CDCA) signal. Consequently, PC deficiency results in activation of CDCA and stimulates cyst growth. Recently, re-expression of PCs in established cysts has been shown to reverse PKD. Thus, the mode of action of PCs resembles a 'counterbalance in cruise control' to maintain lumen diameter within a designated range. Herein we review recent studies that point to novel arenas for future PC research with therapeutic potential for ADPKD.