

## Mammalian Target of Rapamycin (mTOR) Inhibition in Polycystic Kidney Disease (PKD): from Bench to Bedside

Charles L. Edelstein MD, PhD.

Professor of Medicine, University of Colorado, Denver, Colorado USA.

Autosomal Dominant Polycystic kidney Disease (ADPKD) is the most common life threatening hereditary disorder affecting up to 1 in 400 individuals. ADPKD occurs worldwide and in all races and ethnic groups. ADPKD accounts for 4% of ESRD in the USA and 8–10% in Europe and Australia. The most important abnormality in the kidney of ADPKD patients is an increase in proliferation of the tubular epithelial cells lining the cysts as well as increased proliferation of noncystic tubular epithelium. Activation of the mTOR signaling pathway results in increased cell proliferation. Recent studies suggest abnormalities of the mTOR signaling pathway in polycystic kidney disease. Sirolimus (Rapamycin) and Everolimus are FDA-approved drugs for immunosuppression after organ transplantation and treatment of renal cell cancer. mTOR inhibition with Sirolimus or Everolimus results in attenuation of cyst formation and kidney failure in rat and mouse models of polycystic kidney disease. Based on the impressive rodent studies with Everolimus or Sirolimus in PKD, human studies were performed. However, 2 recent studies published in the New England Journal of Medicine of 433 ADPKD patients treated with Everolimus or placebo and 100 ADPKD patients treated with Sirolimus or placebo were unimpressive. Also, in these studies, the side effect profile of Everolimus or Sirolimus was high in ADPKD patients. mTOR exists as two complexes, mTOR complex 1 and 2. Sirolimus and Everolimus inhibit mTORC1. While there are many reasons why Sirolimus or Everolimus may not have worked in humans, one possibility is that there is activation of pro-proliferative mTORC2 pathway, that is Sirolimus independent, in ADPKD. Our studies in rats and mice with PKD demonstrate activation of the mTORC2 pathway. In MDCK cells in culture that form cysts, knockdown of mTORC2 using a silencing hairpin RNA (shRNA) resulted in smaller cysts. A new generation of mTOR inhibitors called mTOR kinase inhibitors or TORCs that inhibit both mTORC1 and 2 are being tested in cancer. In preliminary studies, the TORC, PP242, injected into PKD rats or an antisense oligonucleotide against mTOR injected into PKD mice resulted in inhibition of mTORC1 and 2, a decrease in cyst volume density and improved renal function. In summary there is activation of the mTORC2 pathway in animal models of PKD. mTOR kinase inhibitors or TORCs that inhibit both mTORC1 and 2 may represent a future therapy for ADPKD.