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TITLE: Cellular Energy Pathways as Novel Targets for the Therapy of Autosomal Dominant Polycystic Kidney Disease

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14. ABSTRACT
Autosomal dominant polycystic kidney disease (ADPKD) is a common inherited disorder where patients, over the course of decades, develop large fluid filled cysts that damage the normal kidney tissue and can lead ultimately to kidney failure that necessitates transplantation or dialysis. There are currently no FDA-approved medications for this condition. Recent research reveals that the formation of cysts is due in part both to inappropriate cell growth, fluid secretion, and dysregulation of cellular energy metabolism. The enzyme AMPK regulates a number of cellular pathways, including these disease-causing features. Drugs that activate AMPK, therefore, may constitute an effective therapeutic option for slowing or preventing cyst growth in ADPKD. This research project is aimed at examining the potential of approved, widely used, inexpensive and low-toxicity drugs that can activate AMPK (metformin, simvastatin, and salicylates) and or promote oxidative metabolism (dichloroacetic acid) as potential therapies for the treatment of ADPKD. During this past research period, we measured and analyzed various metabolomic biomarkers in samples derived from cell lysates and urine and continued collecting cyst growth data in ADPKD *in vitro* cell culture models and urine specimens derived from a broad cross-section of patients with ADPKD. We also began collecting *in vivo* data by performing dose-ranging studies of metformin and salicylates in mice.

15. SUBJECT TERMS
Autosomal Dominant Polycystic Kidney Disease, Polycystins, Metformin, Statins, Salicylates, Dichloroacetic acid, AMP-activated Protein Kinase, Biomarkers, Metabolism, Mass Spectrometry

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