**Summary:**
Lonidamine derivatives can be used to inhibit Hsp90 and, therefore, treat, prevent and/or inhibit abnormal cell growth with a favorable toxicity profile

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**Overview:**
A number of renal cystic diseases, including Von Hippel-Lindau (VHL), tuberous sclerosis (TSC), polycystic kidney disease (PKD), and acquired cystic disease (AcCD) are characterized by epithelial neoplastic growth, cyst formation and enlargement, and progression to adenoma and various malignancies, including oncocytoma, clear cell carcinoma, and papillary renal cell carcinoma. While the degree varies to which these disorders progress to metastasis, they all have in common 1) cyst formation, 2) neoplastic growth, and 3) tumor formation.

Our in-vivo and in-vitro studies to date have focused on PKD, in particular autosomal dominant polycystic kidney disease (ADPKD). ADPKD is characterized by abnormal proliferative growth of large epithelial-lined cysts from the nephrons and collecting ducts of affected kidneys. ADPKD is an inherited disease, affecting one in 500-1,000 individuals. Two genes give rise to ADPKD in humans – mutations in PKD1 cause ~85% of ADPKD cases and mutations in PKD2 cause ~15% of ADPKD cases. A less-common form of ARPKD is caused by mutations in the PKHD1 (polycystic kidney and hepatic disease-1) gene.

Cyst growth occurs slowly over decades. Eventually the cystic kidneys fail in about half of affected individuals by the time they reach their 50’s. If cyst growth and enlargement could be slowed, renal failure could be put off by years or even decades, thus effectively delaying or preventing end-stage renal disease.

**Benefits:**
Small molecule inhibitors of Hsp90 inhibit Hsp90 client proteins CFTR and B-Raf, thereby slowing cyst enlargement and preserving kidney function in a dose-dependent manner in patients with polycystic kidney disease (PKD). CFTR and B-Raf have been implicated in both cyst proliferation and fluid secretion in PKD.

**How it Works:**
Using a metanephric mouse model with CFTR mutant mice (Pkd1 -/- : Cftr -/-), our data indicates that cyst formation is stimulated by activation of the CFTR chloride channel on the apical membrane of cyst-lining epithelial cells, thus allowing net chloride secretion and ultimately increased fluid transport into the cyst. cAMP activation of CFTR and B-Raf1 both stimulates cyst proliferation and inhibits the proliferation of normal cells.

Our studies are the first to test Lonidamine and its derivatives as a therapy for PKD, and these are the first studies to test an Hsp90 inhibitor on PKD.

**Why it is better:**
There is currently no cure for PKD. Transplant is an option generally only available to those in end stage renal disease (ESRD). Slowing cyst growth and proliferation could effectively delay or prevent ESRD.

**Applications:**
Several client proteins of Hsp90 are directly associated with uncontrolled cell proliferation states, including the six hallmarks of cancer – self-sufficiency in growth signals, sensitivity to anti-growth signals, evasion of apoptosis, unlimited replication potential, sustained angiogenesis, and tissue invasion/metastasis. As such, our Hsp90 inhibitors could be tested not just in PKD, but several other disease states that involve uncontrolled or abnormal cell proliferation.

**Patents:**
US 8,362,031

**Additional Web Content:**
Contact the inventor, Dr. Jim Calvet

**Tags:**
Hsp90, CFTR, Polycystic Kidney Disease