Project Summary

The Von Hippel-Lindau (*VHL*) tumor-suppressor gene is mutated/lost in about 90% of Clear Cell Renal Cell Carcinomas (CC-RCCs). Because *VHL*-deficient CC-RCCs resist current therapies and frequently metastasize, identifying effective new therapies will be crucial for treatment of CC-RCC patients. By screening the Library of Pharmacologically Active Compounds, we identified the Rho-associated protein kinase (ROCK) inhibitor Y-27632, which selectively targets *VHL*-deficient cells. Our follow-up *in vitro* experiments have shown that knockdown of Rho GTPase C (RhoC) and ROCK1 leads to *VHL*-deficient CC-RCC death and proliferation defect. In this proposal, we **hypothesize** that *VHL* loss leads to over-activation of the Rho/ROCK pathway due to the loss of RhoC/VHL interaction. We further **hypothesize** that targeting the Rho/ROCK pathway *in vivo* will lead to suppression of *VHL*-deficient tumors with minimal toxicity to normal tissues. We will test these hypotheses through the following specific aims: **(1) To determine the mechanism of the synthetic lethal interaction between *VHL* deficiency and ROCK inhibition in CC-RCC; (2) To assess the therapeutic potential of Rho/ROCK inhibitors *in vivo.*** Under Aim 1 we will assess the impact of inhibition of upstream ROCK regulators on proliferation/survival of *VHL*-deficient CC-RCC. We will then further investigate the effect of *VHL* deficiency on Rho expression and activity. Under Aim 2 we will test the effect of Rho/ROCK inhibitors on primary tumor growth and metastasis *in vivo* using an orthotopic mouse model of CC-RCC. We expect this project to yield important results and identify a new class of therapeutics for CC-RCC.