Ruhee Dere, PhD
Assistant Professor
Center for Precision Environmental Health

Targeting Skp2/Ck1 to Restore Nuclear p27 in Cancers with Mislocalized p27

I am currently an Assistant Professor in the Center for Precision Environmental Health at Baylor College of Medicine. I received my Ph.D. from Texas A&M University at the Institute of Biosciences and Technology in Houston. It was as a postdoctoral fellow, with Dr. Cheryl Walker, a leading expert in the field of renal cystic diseases, and Tuberous Sclerosis Complex (TSC) that I investigated the mechanism by which polycystin-1, involved in Polycystic Kidney Disease (PKD), regulated TSC2 (tuberin) a tumor suppressor mutated in TSC. This is when I found my way into the world of renal cell carcinoma and was intrigued as to the mechanisms by which early loss of chromosome 3p and co-deletion of several tumor suppressors contributed to renal cell carcinoma (RCC). We linked loss of primary cilia in VHL (von Hippel Lindau) disease to the activation of a □-catenin and Aurora kinase A (AURKA) signaling pathway. Most recently, we made the discovery of AURKA as a direct and likely oxygen-independent target of VHL which was hugely exciting as it established a function for VHL in both normoxia and hypoxia. Given the role of VHL in regulating microtubules and our recent findings establishing the novel role of the epigenetic modifier SETD2 (Set-domain containing 2) in methylating microtubules, we are currently focusing on understanding and targeting novel pathways downstream of VHL that could rescue cytoskeletal defects in RCC. My interests in crosstalk between pathways and proteins involved in renal cell carcinogenesis, has led to several collaborations one of which I will be detailing in this talk.

Abstract: The tumor suppressor p27, a nuclear cyclin-dependent kinase (Cdk) inhibitor, is often mislocalized to the cytoplasm in cancers such as endometrial cancer (EC) and renal cell carcinoma (RCC). Cytoplasmic p27 serves an oncogenic role actively promoting tumorigenesis and is considered an adverse prognostic marker in solid tumors. We used a novel strategy targeting the interaction pocket of the E3 ubiquitin ligase (Skp2/Ck1) responsible for binding nuclear p27 and promoting p27 turnover. An innovative in silico predictive modeling approach was utilized to virtually screen small molecules for their ability to bind the Skp2-p27 interaction pocket, predicting an inability of this ubiquitin ligase to ultimately degrade p27.

The virtual screen identified 5000 ‘hits’ which were individually evaluated for their docked conformation, binding affinities, and chemotypes leading to the selection of 27 unique compounds. The virtual ‘hits’ combined with chemically similar molecules were subject to a high-content screening assay to identify probes that exclusively lead to elevated nuclear p27 without increasing cytoplasmic p27 levels. Five small molecules were ultimately chosen from this primary screen to advance through a battery of secondary biochemical validation assays. We confirmed the ability of these probes to increase nuclear p27, decrease p27 ubiquitination and inhibit cell cycle progression. These studies lead to the identification of Compound 276 which progressed to preclinical pharmacokinetic and pharmacodynamic studies at the CPRIT-funded core at Texas Southern University. These studies highlighted the feasibility of in silico modeling to screen a lager cohort of small molecules that specifically abrogated Skp2 binding to p27, which informed subsequent primary and secondary screens that identified a small molecule with potential value for clinical intervention.