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Location:  
Biomedical Sciences Partnership Building (BSPB) | 475 N. 5th Street, Phoenix, AZ 85004; Rooms E113/115

Presentation: 
Title: “NRF2-based therapeutics for disease prevention and intervention”

Q&A:  
2:20 – 2:50 PM  
2:50 – 2:55 PM

Abstract: Nuclear factor erythroid 2-like 2 (NRF2) is a transcription factor that confers cellular protection against oxidative, proteotoxic and metabolic stress. NRF2 has been shown to act as a master regulator, controlling many cellular processes via crosstalk with other signaling pathways. Through detailed mechanistic investigations, KEAP1 has been shown to be the primary regulator of NRF2 by functioning as a substrate adaptor of the KEAP1-CUL3-RBX1 ubiquitin ligase. KEAP1 acts as a sensor for electrophilic or redox active xenobiotic agents through a series of redox sensing cysteines, most prominently Cys151. This KEAP1 action controls NRF2 protein levels to maintain cellular redox homeostasis. In normal cells, activation of NRF2 by chemopreventive compounds confers protection against cancer. Therefore, a great deal of effort has been geared toward identification of small synthetic molecules or natural products that inactivate KEAP1-CUL3-RBX1 and increase NRF2 levels. We have discovered many chemopreventive small molecules that activate NRF2 and are effective for disease prevention. Most of these NRF2 inducers activate NRF2 through covalent adduction to KEAP1-C151. However, many of these reactive compounds suffer from off-target effects. New strategies in developing a new class of NRF2 inducers with less off-target toxicity will be discussed.

Functional analyses of NRF2 have demonstrated a dual role for NRF2 in cancer. In 2008 we presented the unprecedented concept of the dark side of NRF2, demonstrating that NRF2 promotes cancer progression and chemoresistance. As such, cancer cells with high expression of NRF2 are more resistant to cancer treatment, and clinically these patients have a poor prognosis. We provided strong evidence that inhibiting NRF2 renders cancer cells more susceptible to chemotherapeutic drugs. This work has led to a paradigm shift in viewing NRF2 as a “tumor suppressor” to an “oncogene”. These studies, revealing the dark side of NRF2, strongly argue for the need to develop small molecule inhibitors of NRF2. Building on this idea, we reported the first rationally discovered compound, brusatol, that inhibits the NRF2 pathway. Brusatol was able to overcome both intrinsic and acquired chemoresistance both in vitro and in vivo (KrasG12D lung cancer model). However, further work revealed that brusatol might have off-target effects at high doses, in addition to being a synthetically challenging, complex natural product, limiting the potential of developing brusatol into a drug. Since then, several other NRF2 inhibitors have been reported. However, to date, there are no inhibitors that directly target NRF2 with a defined mode of action in development. In this talk, I will discuss the challenge and our innovative multi-tier, targeted screening strategy in identifying NRF2-targeted inhibitors.