The V-Foundation for Cancer Research

V-Scholar Grant Application

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Title

Identification of ubiquitin signaling networks as novel avenues for therapeutic intervention

Abstract

The ubiquitin proteasome system (UPS) provides new clues as to cancer etiology and progression and suggests new avenues for therapy. These points are exemplified by regulation of the tumor suppressor p53. Enhanced degradation of p53 by its cognate E3 ligase Mdm2, or the human papillomavirus E6 oncoprotein, contributes to cancer and small molecule Mdm2 inhibitors stabilize p53, re-enforcing its tumor suppressive activity. UPS targeting as a therapeutic strategy faces two significant challenges: development of inhibitors that inactivate specific enzymes and determination of which nodes to target (e.g. Mdm2-p53). Recent identification of small-molecule inhibitors to numerous ligases demonstrates the feasibility of targeting the UPS. The latter challenge will be approached in this proposal by globally interrogating ubiquitin signaling networks. To address the technological challenges associated with globally examining UPS signaling, I developed genetic and proteomic technologies that comprehensively assess changes in protein ubiquitination and degradation. My parallel application of these large-scale discovery platforms identified hundreds of proteins regulated by the Cullin Ring Ligases, the largest human E3 ligase family. This study represents the most comprehensive identification of E3 ligase substrates ever preformed. My long term goal is to pharmacologically manipulate the abundance of key cellular proteins by modulating the activity of specific UPS components that control their abundance. An unbiased assessment of ubiquitin signaling networks and the connection of ligases with their cognate substrates is essential to classify which UPS enzymes are worthy therapeutic targets for drug development and clinical intervention.