"Small Molecule Inhibitors of the Ubiquitin Pathway in Antagonizing Skin Carcinogenesis"

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Abstract: The *CUL4A* ubiquitin ligase gene is frequently found amplified or overexpressed in a wide variety of tumor types, including breast and skin cancers. While recent studies identified the components of the multimeric CUL4A E3 ligase complex and several cellular targets, the role of CUL4A in tumorigenesis remains largely elusive. We and others showed that CUL4A plays an inhibitory role in nucleotide excision repair through targeted degradation of DNA damage sensors DDB1 and DDB2. Importantly, our skin-specific CUL4A knockout mice are resistant to UV- and chemical carcinogen-induced skin cancer, and are healthy and display no abnormalities, suggesting that CUL4A is an attractive target for cancer prevention. The primary objective is to identify synthetic inhibitors of the CUL4A ubiquitin ligase through high-throughput screening of chemical libraries or phage display peptide libraries. We propose to combine the biochemical, cell biological, and genetic approaches in Dr. Pengbo Zhou's lab and the extensive high-throughput screening expertise of Dr. Yueming Li's group, and the availability of the state-of-the-art chemical and phage display libraries and HTS core facility at MSKCC to pursue the following two specific aims: (1) To develop and optimize an HTS assay for CUL4A-DDB1 interaction, with specific emphasis on interrogating their direct binding interface; (2) To develop quantitative HTS assays to identify small molecules that disrupt DDB1-CUL4A interaction and ubiquitin ligase activity. Successful completion of the proposed studies will represent the first step towards evaluating the efficacy of pharmacological CUL4A inhibition as an effective approach for cancer prevention and intervention.