"Sensitizing shRNA Screen for Molecular Targets in CDK4/CDK6-Based Cancer Therapy"

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Abstract: Dysregulation of the cell cycle is central to tumorigenesis. Targeting the cell cycle in combination with cytotoxic killing, therefore, is a rational approach to cancer therapy. Emerging evidence in human cancers further reinforces the critical importance of controlling cyclin-dependent kinase (CDK)4 and CDK6 in cancer treatment, but success with broad-spectrum CDK inhibitors has been modest due to lack of selectivity and high toxicity. By inhibiting CDK4/CDK6 with the only known selective inhibitor, PD 0332991 (PD), we have developed a novel strategy to both inhibit proliferation of tumor cells and prime them for cytotoxic killing in multiple myeloma (MM), lymphoma and leukemia. Induction of G1 arrest by inhibition of CDK4/CDK6 leads to time-dependent uncoupling of gene expression from the cell cycle, and release of the G1 block effectively synchronizes progression to S phase, restores the temporal gene expression program and profoundly enhances cytotoxic killing. Our long-term goal is to advance mechanism-based cancer therapy through targeting the cell cycle. To achieve this goal, we will identify molecular targets required to enhance apoptosis in S phase by genome-scale pooled shRNA screen and validation in animal models of myeloma and leukemia. As PD is orally bio-available, potent and low in toxicity, our approach has led to a phase I/II clinical trial targeting CDK4/CDK6 in combination therapy in MM. We will therefore directly apply our findings to refine targeting CDK4/6 in MM. In conjunction with novel mechanistic insights that emerge from this study, we will also advance targeting CDK4/CDK6 in leukemia and potentially other cancers.