"Application of Genomics to Developmental Therapeutics of Melanoma"

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Abstract: The stratification of cancer based on genetic and molecular criteria offers potential for remarkable improvements in treatment. However, meaningful advances in treatment of solid tumors have been encumbered by a paucity of tractable and clinically relevant experimental systems. In this proposal, we have marshaled expertise from the Broad Institute, Cold Spring Harbor Laboratory and Memorial Sloan-Kettering Cancer Center in genomics, signal transduction, and melanoma biology and therapeutics. We will perform detailed genomic and molecular characterization of >300 clinically annotated, short-term culture melanoma lines, together with ~100 clinically matched melanoma specimens. A subset of ~60 cell lines will be identified that encompasses the range of (epi)genetic and molecular diversity within melanoma. Using this panel, we will seek to identify key genetic and epigenetic perturbations that offer appealing therapeutic avenues, through interrogation of melanoma cells with selective inhibitors of MEK, RAF, PI3K and AKT kinases. Results with inhibitors will be integrated with genomic data to: i) determine the biologic effects of pathway inhibition as a function of the ensemble of mutations in the MAPK and AKT signaling pathways; ii) identify molecular predictors and cellular modifiers of drug efficacy; and iii) characterize adaptive/feedback responses in different genetic contexts. Finally, we will examine tumor samples and primary cultures from melanoma patients treated with inhibitors of these same pathways to assess whether molecular factors credentialed in the cell line studies modify therapeutic response or resistance in patients' tumors. Together, these studies should pave the way for an unprecedented convergence between genomics and clinical treatment that informs rational therapy for melanoma and other solid tumors.