“Development of Mechanism-Based Therapies for the Treatment of Metastatic Melanoma”

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Abstract: This proposal is based on findings from our previous Starr Cancer Consortium (SCC) award on the molecular biology of melanoma. We found that RAF inhibitors inhibit ERK signaling selectively in tumors with mutant BRAF, but activate it in other cells. These discoveries informed the trial of the RAF inhibitor PLX4032, which achieved a remarkable 70% partial response rate in patients with mutant BRAF melanoma. However, the median duration of response is only nine months. Thus, the next critical issues are how to enhance the extent and duration of responses and overcome acquired resistance to RAF inhibition. Our discoveries about melanoma genetics and the biochemistry of RAF signaling, together with powerful new technologies implemented by our team, will allow comprehensive understanding of *de novo* and acquired drug resistance and the development of new therapeutic strategies. We have assembled a team of scientists and clinicians from two SCC institutions to perform systematic preclinical characterization of genetics and dysregulated signaling in melanoma, lead the phase 3 trial of the RAF inhibitor, and validate our findings in tissue from treated patients. Our elucidation of the unique mechanism of action of RAF inhibitors allows us to understand their greater efficacy compared to MEK inhibitors and suggests strategies for combination therapies to improve response and evade resistance. The translational goal is the long term control of metastatic melanoma, a goal that now seems conceivable.