Overcoming Paclitaxel Resistance in Melanoma
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Melanoma is the most aggressive form of skin cancer. Patients with metastatic disease have a dismal prognosis, and patient outcomes are not significantly improved by treatment with systemic therapies. RNA interference (RNAi) libraries are powerful tools to systematically interrogate the biological effects of inhibition of any gene. Experiments using siRNA libraries allow for the identification of therapeutic approaches that may be undertaken using available inhibitors, or identify targets for which inhibitors should be developed. This approach has recently been utilized using a human lung cancer model, and identified a number of targets that induce synthetic lethality with paclitaxel. We have characterized a panel of melanoma cell lines, and have identified two cell lines with high-grade resistance to paclitaxel in vitro. In preliminary experiments, we have evidence that synthetic lethal targets in the melanoma cell lines may not overlap with the findings in the lung cancer model.

Our long-term goal is to identify rational therapeutic approaches to overcome chemoresistance in metastatic melanoma. The hypothesis of this project is that inhibition of specific proteins will overcome resistance to paclitaxel in melanoma, and result in therapeutic combinations that will improve clinical outcomes for patients with metastatic disease. In order to test this hypothesis, we propose to perform a paclitaxel synthetic lethality screen with the Dharmacon whole-genome siRNA library in conjunction with the WM2664 human melanoma cell line. This proposal includes the optimization of experimental conditions for the performance of this screen, and plans for confirmatory experiments to be conducted on candidate targets in a focused secondary screen. In addition to identifying therapeutic combinations to overcome paclitaxel resistance in patients, the results of these studies may also suggest candidate biomarkers for taxane resistance that may be evaluated both retrospectively in clinical specimens, or prospectively in upcoming clinical trials of taxanes being conducted at The University of Texas – M. D. Anderson Cancer Center. The results of this project should provide preliminary data and hypotheses for which additional funding can be applied to further develop approaches to improve our understanding of the pathogenesis of melanoma. Ultimately we hope that the information derived from this study may be applied directly to patients in the setting of clinical trials.