"Studying Tumor Progression and Treatment Resistance Using Focused Re-sequencing of High-value Gene Sets in Mouse Models of Human Lung Adenocarcinoma"

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Abstract: The Cancer Genome Atlas (TCGA) and related projects have been conceived to identify the complete set of mutations in human tumors. The cost of such projects has limited their application to only human disease, in which only a single point in a tumor's developmental history can be practically analyzed. Mouse models of human cancer have the benefits that the underlying genetics of the tumor can be controlled and multiple, genetically similar samples can be followed throughout their developmental history. These models importantly exhibit gene expression profiles, patterns of progression, and treatment responses that are similar to human tumors. Recently, we have developed focused re-sequencing strategies, which combine hybrid selection of genomic subsets on microarrays with second-generation sequencing platforms. These strategies permit a cost-effective assessment of the mutational state of a specified, high value fraction of the target genome. The goal of this program is to develop and refine a platform for *in situ* exon capture coupled to massively parallel sequencing in order to characterize the mutational state of the murine lung adenocarcinoma genome. In contrast to human studies, mutations can be 'mapped' to specific stages during tumor development and treatment response in order to elucidate the genetic underpinnings of tumor progression and drug-resistance. Another critical advantage of mouse models is the ability to functionally validate identified mutations within the same system. We anticipate that these studies will offer fundamental insights into the genetic basis of tumor progression and treatment response, and identify novel therapeutic targets in human cancer.