EGFR inhibition in lung cancer: resistance, sensitization, and combination therapy

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Abstract: EGFR inhibitors have revolutionized the treatment of lung cancers bearing EGFR mutations, but acquired resistance continues to plague treatment of these patients. The goal of this study is to use the power of patient-focused genomics coupled with high-throughput functional genomic approaches to enable both the development of better on-target drugs against mutant EGFR as well as combinations that will enable complete treatment of this class of cancers.

Our proposal brings together the complementary expertise of teams at Memorial Sloan Kettering Cancer Center, led by Drs. Ladanyi and Yu, and the Broad Institute, led by Dr. Meyerson. In our first aim, we use genomic analysis of paired pre-treatment and post-relapse biopsy specimens to identify both *cis* and *trans* mechanisms of resistance. Second, we use high-throughput perturbations including CRISPR and transposon insertional mutagenesis to identify both gain-of- and loss-of-function genetic modulators of osimertinib response, to identify *trans* mechanisms of resistance and sensitization. Third, we use saturated mutagenesis to acquire a comprehensive understanding of the mechanisms by which EGFR is activated and becomes resistant to osimertinib. We then integrate these analyses to provide a mechanistic view of EGFR activation and inhibition, and to use this knowledge to consider potential combination targets.

Through this study, we expect to deepen our knowledge of the regulation of EGFR in lung adenocarcinoma and to further advance the treatment of this subset of cancers.