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Title: Exploitation of Vulnerabilities Created by Oncogenic p53 In Non-small Cell Lung Carcinoma

The prognosis for non-small cell lung cancer (NSCLC) patients is poor with the five-year survival rate of patients with metastatic NSCLC at 8% (https://www.cancer.org/cancer/lung-cancer/detection-diagnosis-staging/survivalrates.html), indicating poor efficacy of current treatments. The tumor suppressor p53 is mutated in 69% of NSCLC cases and the majority of p53 single amino acid substitution mutants have dominant oncogenic properties. Oncogenic p53-expressing tumor cells show dependency on the mutant protein for their growth and survival, such that the oncogenic mutant form of p53 is a desirable therapeutic target for NSCLC. The long-term goal of this program is to develop safe and effective targeted NSCLC therapies that leverage vulnerabilities generated by oncogenic p53 expression. We have demonstrated that the tumorigenicity of NSCLC cells in mice can be blocked by targeting vulnerabilities specific to cells expressing oncogenic p53 not present in normal cells that express wild-type (WT) p53, leading the way to new and powerful strategies for treating the majority of NSCLC patients. The overall hypothesis of this program is that functional changes in NSCLC cells that occur as a result of oncogenic p53 create multiple vulnerabilities and susceptibilities to specific therapeutic approaches that do not harm normal cells. The goals will be met by the following three complementary and interactive aims:

1. (a) Investigate the connection between proteotoxic and oxidative stress in PI-treated Onc-p53 NSCLC cells. (b) Investigate the mechanism and strategies for therapeutic targeting of BH3-dependent apoptosis in PI treated Onc-p53 NSCLC cells. (c) Investigate the therapeutic potential of PIs in Onc-p53 NSCLC. (Project 1)
2. (a) Examine two of the identified oncogenic p53 inhibitors (Onc p53TAIns), Gloxazone and Benzamide, for their ability to specifically inhibit survival or proliferation of lung cancer cells with oncogenic p53. (b) Identify the oncogenic steps targeted by Gloxazone and Benzamide. (c) Examine abilities of Gloxazone and Benzamide to specifically inhibit oncogenic p53-driven tumor formation. (Project 2)
3. Investigate a primary and metastatic NSCLC elimination strategy using oncogenic p53-specific immune activation by IL-12 and IL-15 using exosome delivery systems in mouse tumor models. (Project 3)

Impact: The program will forge inter-related therapeutic strategies that are radically different from current strategies, based on oncogenic p53-induced activation of unique pathways in cancer cells that can be specifically targeted without affecting the normal cells with WT p53. The strength of the program is its novel multi-prong approach. We anticipate the results of our program will lead to a paradigm shift for new and effective therapies
for treating NSCLC.