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**Title: INHIBITION OF PRECANCEROUS TRANSFORMATION VIA DRUG-INDUCED P53 ACTIVATION**

**Abstract**

Pancreatic ductal adenocarcinoma (PDAC) is currently the third leading cause of cancer deaths in the US, and has a 5-year survival rate of less than 10%. This low survival rate is largely due to low rates of early detection, and the lack of treatments capable of inhibiting disease progression. Patients suffering from pancreatitis are prone to acquire precursor lesions known as pancreatic intraepithelial neoplasia (PanIN), and not surprisingly, have an increased risk of developing PDAC. Notably, the lack of treatment options for these patients reinforces the need for strategies that could resolve pancreatic damage and stop disease progression. Towards this end, we have recently shown that administration of Nutlin-3a (a non-genotoxic inducer of p53) in mouse models of PDAC confers resistance to metaplastic transformation, reduces the proliferation of PanIN lesions, and lowers levels of Erk phosphorylation. We have also observed expression of p53 in the embryonic mouse pancreas, suggesting a novel role of p53 in pancreatic differentiation. Based on our findings, we hypothesize that p53 activation can signal for the redifferentiation of metaplastic cells, and suppress Kras signaling in PanIN lesions. Our studies will define the role of p53 in pancreatic differentiation and the potential of pharmacological p53 activation for the treatment for pancreatitis and prevention of PDAC.