SYNERGISM OF NELFINAVIR AND CURCUMIN COMBINATION THERAPY IN PANCREATIC CANCER CELLS

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Background: Pancreatic adenocarcinoma (PDAC) is known for its high mortality rates and poor response to treatment. Molecular studies have implicated several pathways influencing tumoriogenesis for which many new treatment options are based. The phosphatidylinositol 3-kinase (PI3K)-Akt pathway is a prototypic survival pathway and has been shown to have effects on proliferation, adhesion, invasion, and apoptosis in multiple cancers, including PDAC. Nelfinavir, an FDA approved human immunodeficiency virus protease inhibitor, has been shown to downregulate this pathway by decreasing Akt phosphorylation via endoplasmic reticulum-based stress and induces autophagy and apoptosis *in vivo*. Diferuloylmethane (curcumin) is a naturally occurring flavinoid derived from *Curcuma longa* which has proapoptotic effects, and is currently in phase II clinical trials for advanced PDAC. Curcumin is also thought to have antitumor effects by indirectly downregulating the PI3K-Akt pathway by *MDM2* oncogene suppression. While both of these drugs have been shown to have low toxicity and are already FDA approved for other indications, low bioavailability and poor pharmacokinetics have limited their utility in PDAC. Here, we have tested the hypothesis that combination treatment of nelfinavir and curcumin on pancreatic cancer cells manifests as synergistic antitumor effect *in vitro*, allowing for lower concentrations and increased efficacy.

Methods: The cytotoxic effects of nelfinavir and curcumin combination were tested in three pancreatic cancer cell lines: PL-45, Panc-1, and MiaPaCa2 by MTT (3-(4,5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide) cell viability assays.

Results: All pancreatic cancer cells lines showed increases in cytotoxicity with increases in concentration when exposed to nelfinavir (range 0.5 µM to 50 µM) and curcumin (range 1µM to 100 µM. When used in combination, greater cytotoxicity was exhibited at low concentrations of nelfinavir and curcumin when compared with same monotherapy concentration.

Conclusion: This study provided evidence that combination therapy with nelfinavir and curcumin has synergistic antitumor effects than monotherapy with either drug, and allows for lower concentrations of both drugs.