Novel Drug Combinations in Non-Small Cell Lung Cancer

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Non-small cell lung cancer (NSCLC) is a leading cancer worldwide, with traditional therapies still resulting in low survival rates. The focus is shifting towards biomarker identification, to be used as targets for anti-cancer drugs. The Mammalian Target of Rapamycin (mTOR) and the Translational Controlled Tumour Protein (TCTP) are essential proteins for cell growth and proliferation, and are known to be overexpressed in cancer cells. mTOR promotes cell proliferation through the Eukaryotic Translation Initiation Factor (eIF4E), which in turn is involved in TCTP translation. In addition, mTOR is known to be involved in TCTP synthesis, while TCTP is an indirect activator of mTOR. The aim of this research was to test a novel dual therapy, targeting mTOR and TCTP. INK-128 is a dual mTOR inhibitor, currently in clinical trials on patients with various types of cancer, including NSCLC. TCTP Antisense Oligonucleotide (ASO) is an oligonucleotide currently under patent by collaborators of the University of Malta from the 'Centre de Recherche en Cancérologie de Marseille', which targets TCTP. TCTP ASO has been tested both *in vitro* and *in vivo*, but not on NSCLC.

The effect of INK-128 and TCTP ASO on the cell viability and eIF4E was tested on NSCLC cell lines *in vitro*, separately and in combination. The effect of a varying concentration of INK-128, ranging from 0.01 μM to 5 μM, was tested on SK-MES-1, H460 and A549 cell lines. Cell viability data was gathered through viability assays following 24 to 72 hours, while eIF4E was monitored through eIF4E Enzyme-Linked Immunosorbent Assays (ELISAs) following 24 hours. Treatment with 0.1 μM TCTP ASO was performed on the H460 cell line. Cell viability, eIF4E and TCTP levels were monitored following 24 hours, with the latter data achieved by means of a TCTP ELISA. A 1 μM TCTP ASO treatment was also performed, prior to the eIF4E ELISAs. The dual therapy was tested on H460 cells. INK-128 and TCTP ASO treatments at 0.1 μM and 1 μM concentrations were followed by eIF4E ELISAs. On the other hand, treatments with 0.01 μM INK-128 / 0.1 μM TCTP ASO and 1 μM INK-128 / 0.1 μM TCTP ASO were followed by cell viability assays. Independent sample t-tests and non-linear regression analyses were performed on these results.

INK-128 decreased the cell viability of SK-MES-1, H460 and A549 cell lines, with IC_{50} values of 2.750 μM, 0.252 μM and 0.008 μM respectively. INK-128 decreased the levels of eIF4E in H460 cells, with an IC_{50} of 0.080 μM. Treatment with TCTP ASO decreased the TCTP in H460 cells by 48%, as well as eIF4E, with the IC_{50} for eIF4E being 0.209 μM. The dual treatments with INK-128 and TCTP ASO were found to decrease the cell viability. These results were statistically significantly different from the controls, but not different from the respective monotherapies. The combinatory treatment with INK-128 and TCTP led to a decrease in eIF4E levels, with an IC_{50} of 0.043 μM

The monotherapy results of the two drugs indicate that INK-128 was more effective in decreasing the cell viability, while TCTP ASO was more effective in decreasing eIF4E, suggesting that the combination of the two drugs has the potential to target both mTOR and TCTP concurrently, and that therefore the dual therapy has potential as a therapeutic regime against NSCLC cancer.