

Investigating the Changes in Gene Expression of SUM159 Breast Cancer Cells through Application of KPT-9274

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KPT-9274 is a promising orally bioavailable medication that is currently in phase 1 clinical trial for the treatment of human cancer. Its pharmacological action is done through the inhibition of PAK4, a protein kinase that is overexpressed in many human cancer cell types. We focused on SUM159, cells extracted from triple negative breast cancer, due to its high level of PAK4 expression. Our purpose of the project is to understand the cascade of molecular reactions and specific genes directly and indirectly regulated by KPT-9274. Based on the previous finding of KPT-9274 induced apoptosis starting around Day 4, we used Next Generation RNA Sequencing and the Ingenuity Pathway Analysis Program on vehicle and KPT-treated cells at 4 days. Based on the RNA sequencing result, we hypothesized that GADD45a, GADD45b, HMOX1, and KLF6 as the growth inhibitory genes that are upregulated via PAK4 inhibition, and MCL-1 and SESN2 as the growth promoting genes that are downregulated via PAK4 inhibition. quantitative Polymerase Chain Reaction was conducted to validate the RNA expression of the genes, and my project was to carry out western blots to confirm if the protein levels of the genes correspond to the RNA data. At this point, the qPCR data accurately reflected the changes in RNA expression, while the results for western blot must be investigated furthermore. Further studies of conducting more western blots on genes with ambiguous results, and conducting western blots and qPCR on immortalized Mouse Mammary Epithelial Cells (iMMEC) must be conducted to substantiate our hypothesis. Supported by NIH R25ES020721.

