Entrega de l'Abstract

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Títol de la recerca: Preclinical investigations on drug delivery and anti-tumor efficacy against high-grade glioma by combination therapy using small molecular inhibitors targeting Wee1 and PARP with DNA-damaging agents

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Abstract (màxim 500 paraules):

Glioblastoma Multiforme is one of the most aggressive human cancers and the most common primary brain tumor. Despite considerable work in recent years in several pre-clinical and clinical trials, not much therapeutical improvement has been reached. The standard-of-care consists of surgical resection followed by radiotherapy (RT) with adjuvant temozolomide (TMZ) and chemotherapy (both DNA damaging agents). Hence, other strategies have to be sought to improve chemo-radiation therapy in GBM patients. Potential of the current therapy might be enhanced by both inhibition of DNA-repair pathways and the G2-checkpoint abrogation, thus avoiding the ability to repair treatment-induced DNA damage. The present study focuses on the *in vitro* efficiency of both PARP and Wee1 inhibition, screening its potency either as a single agent or in combination with TMZ plus radiation. Experiments are also conducted using Elacridar in combination with the other drugs. Elacridar, a P-gp and BCRP inhibitor, might improve the drug transport through the blood brain barrier.

In this study the DNA-damaging agents TMZ and radiation, the PARP inhibitor ABT-888 and the Wee1 inhibitors MK-1775 and PD-0166285 are tested for their potency in *in vitro* assays using various GBM and human cell lines. Cytotoxicity experiments and Clonogenic assays are conducted to measure inhibitory effect on cell proliferation after 2/5 days exposure and in a long term period respectively. Western blot analysis is performed after 4-h exposure to all the agents and assessing of target inhibition using specific antibodies. Caspase analysis is carried out by comparing apoptotic activity in non-treated cells and cells treated with different drug combinations.

Mostly, cells treated with the single inhibitor agents do not show any significance effect in cell proliferation. Only cell lines knock out by Pten or the double knock out Pten/P53 seem to

be much more responsive to the single treatment. Pten KO cell lines were the most synergistic for treatment combinations in all the cases, followed by the double KO Pten/P53. PARP inhibition is successfully achieved for all cell lines, whereas Wee1 inhibition is not clearly seen. Elacridar is slightly improving the target inhibition efficacy of ABT-888; this is due to a higher drug entry to into the cell. ABT-888 in combination with TMZ and radiation allows a better cell proliferation inhibition at long-range, validating the results from the short term experiments.

We can conclude that PARP inhibition is a good option for drug combination therapy in GBM. Cells seem to be responsive to the treatment with ABT-888 and such drug presents a synergistic effect with the radiation. Prominently, Pten-null cell lines treated with all drug combinations are highly more sensitive than the other cell lines used. Elacridar enhanced the ABT-888 efficiency.

Altogether, all the experiments were done on my own. I had the chance of using the cell lines, the drug concentrations and all the drug combinations that I wanted. I can confirm that this work was basically carried out by myself, and all the results I got were also achieved from my experiments. I am so proud to say that this project was so successful, and I hope these results will increase the insight of the GBM. It is also important to mention that some of my results were included in an article (written by my supervisor) which is going to be probably published in a while. It includes the improved therapy on the Pten-null cell lines and the experiments with Elacridar as well. Importantly, this is only a very short summary of all the experiments and results I got.