Título: TUNING RESPONSE TO THERAPY IN PRECLINICAL GL261 GLIOBLASTOMA THROUGH CK2 TARGETING AND TEMOZOLOMIDE METRONOMIC APPROACHES: NON-INVASIVE ASSESSMENT WITH MRI AND MRSI-BASED MOLECULAR IMAGING STRATEGIES

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Resumen: Work described in this thesis deals with the treatment of GL261 preclinical glioblastoma (GBM) growing in C57BL/6 mice, as well as with the non-invasive assessment of response to therapy using magnetic resonance (MR) techniques. The GL261 GBM is an immunocompetent model induced by stereotactic injection of GL261 cells into the striatum of C57BL/6 WT mice. Three different therapeutic agents have been tested in this model: CX-4945®, a protein kinase II (CK2) inhibitor, and two oral alkylating agents commonly used in the clinic for GBM treatment, temozolomide (TMZ) and cyclophosphamide (CPA). CK2 has been described as a potential suitable target for cancer treatment because it contributes to tumour development, proliferation, and apoptosis suppression in cancer. In addition, elevated CK2 expression levels have been demonstrated in several cancer types. Nevertheless, CX-4945, which already reached phase I/II clinical trials, did not produce the expected beneficial effect described by others when applied to our GL261 GBM model. Moreover, the GL261 GBM

treatment with 3 TMZ cycles had been already described by our group with significant survival improvement. Nevertheless, the combined therapy 3 cycle-TMZ+CX-4945, unexpectedly, reverted the beneficial effect of TMZ, which suggested an interference with the immune cycle related with cancer development and treatment. This lead us to consider the use of a metronomic schedule (administration of low and equally spaced doses of drugs without long rest periods in between) described with promising results in the literature. CPA, TMZ and CX-4945 were assessed in a 6-day schedule metronomic schedule at different doses. Among the different strategies evaluated, best results were obtained with the combined metronomic administration, every 6 days, of TMZ and CX-4945 drugs, showing significant improved survival. This also pointed to the probable paticipation of the host mice immune system in therapy response, although further histopathological studies will be needed to fully confirm this hypothesis.

Additional interesting findings were: firstly, a clear peritumoral brain edema appearance during certain stages of chemotherapeutic treatment. Secondly, that the non-invasive method for therapy response assessment based in semi-supervised source analysis of Magnetic Resonance Spectroscopy Imaging (MRSI) data, previously developed in our group with TMZ-treated mice, also proved useful for detecting CPA-induced response in our preclinical model. This would suggest that a common ¿metabolomics responding pattern¿ can be observed under different therapeutic strategies. And thirdly, the necropsy findings in mice cured from GL261 GBM after high TMZ cumulative dosage (480-1400 mg/Kg), which presented relevant lymphoma incidence, suggesting that strategies to decrease the administered dose should be investigated to avoid harmful effects in mice treated with alkylating agents.