



Research Project Proposal
Academic year 2015-2016

Project Nº 11
Title: Pharmacological modulation of histone acetylation and methylation in PTEN haploinsufficient and heterogeneous glioblastoma.
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Summary: Nowadays there is a great interest in tumor heterogeneity. Glioblastoma (GB) is one of the malignant tumors that more clearly shows such heterogeneity, and specially related to PTEN expression, a protein that plays a relevant role in the oncogenesis of this brain tumor. PTEN haploinsufficiency derived from the loss of one of the two alleles of the gene, would reduce CBP histone acetylase expression, increase EZH2 histone methylase expression, and decrease p21 and p27 expression (iCDK), increasing cell growth thereafter. This mechanism might be modulated by panobinostat (iHDAC) and/or DZNep (inhibitor of EZH2). We might assume that panobinostat and/or DZNep might modulate and revert PTEN haploinsufficiency in GB and, as a consequence, re-activate PTEN tumor suppressor function. We pretend to test the expression of proteins of the PTEN-PI3K/AKT signaling pathway, CBP, EZH2, p21 and p27 by immunohistochemistry and western blot in GB cell lines in two different situations: GB +/- for immunohistochemistry of PTEN with haploinsufficiency, and GB +/- for immunohistochemistry of PTEN without haploinsufficiency. Functional in vitro studies (cell migration, clonogenicity assays in soft agar, and colony formation assays) will be performed before and after treatments in order to test the possibility that the treatments would reduce in vitro tumorigenesis.
References <ul style="list-style-type: none">• Ding L, Chen S, Liu P, Pan Y, Zhong J, Regan KM, Wang L, Yu C, Rizzardi A, Cheng L, Zhang J, Schmechel SC, Cheville JC, Van Deursen J, Tindall DJ, Huang H. CBP loss cooperates with PTEN haploinsufficiency to drive prostate cancer: implications for epigenetic therapy. <i>Cancer Res.</i> 2014;74(7):2050-61.• Berger AH, Pandolfi PP. Haplo-insufficiency: a driving force in cancer. <i>J Pathol.</i> 2011;223(2):137-46.• PTEN Inhibited by Acetylation. <i>Sci. STKE</i> 2006, tw310 (2006).
POSSIBILITY OF PhD YES* * (PhD grant required)