ANTITUMOR ACTIVITY OF MIXED TERNARY MONONUCLEAR MG COMPLEX BASED ON VALPROIC ACID WITH 1,10-PHENANTHROLINE IN GLIOBLASTOMA MULTIFORME CELLS.

Julia Vanini [1,4,5]; Francine Bester Damian[4,5,6]; Françoise Dumas [2]; Rafael Roesler [1,4,5]; João Antonio Pêgas Henriques [1,3]; Iuri Marques de Oliveira [1]

[1] Federal University of Rio Grande do Sul, Porto Alegre, RS, Brazil, [2] Université Paris Sud, Faculté de Pharmacie, 92296 Châtenay-Malabry Cedex, France, [3] University of Vale do Taquari, Lajeado, RS, Brazil, [4] Clinical Hospital (CPE-HCPA), Federal University of Rio Grande do Sul, Porto Alegre, RS, Brazil, [5] National Science and Technology Institute for Children's Cancer Biology and Pediatric Oncology-INCT BioOncoPed, Porto Alegre, RS, Brazil, [6] Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre, RS, Brazil.

INTRODUCTION: Glioblastoma multiforme (GBM) is the most common primary brain tumor classified as grade IV malignancy with a low survival rate. Valproic acid (VA) is a drug widely used in the treatment of neurological diseases such as epilepsy, bipolar disorder and schizophrenia. Due to the discovery of its potential to inhibit histone deacetylases (HDACs), VA has become the subject of studies related to anticancer therapy. However, the use of VA has limitations because it causes systemic toxicity. Therefore, the development of new drugs from pre-existing molecules becomes a more effective strategy in order to reduce the side effects of drugs already used in the clinic. **OBJECTIVE:** Thus, in the present work we investigated the cytotoxic and genotoxic potential induced by the magnesium complex based on valproic acid with 1, 10-phenanthroline [$Mg(Valp)_2Phen$] in GBM cells (M059J, U87MG and U251MG). **MATERIALS AND METHODS:** The MTT test was performed to assess cell viability after treatment with the complex. The clonogenic assay was used to assess the ability of the cell lines to form colonies. The comet and micronucleus assays were performed to assess the rate of DNA damage caused by exposure to the derivative. **RESULTS AND CONCLUSION:** The MTT assay and the clonogenic survival showed similarity in the toxicity pattern of the [$Mg(Valp)_2Phen$], which showed more cytotoxicity in tumor cells

than in the non-tumor cell line suggesting selectivity and presented higher cytotoxicity compared to the VA. The results observed in the comet assay and micronucleus test indicate that VA and the [$Mg(Valp)_2Phen$] induced DNA strand breaks formations. Therefore, the results are promising considering the antitumor effects demonstrated by [$Mg(Valp)_2Phen$], which demonstrated higher cytotoxicity and genotoxicity in GBM than in non-tumor cells. Furthermore, cytotoxic and genotoxic effects were more pronounced for [$Mg(Valp)_2Phen$] compared to sodium valproate. Thus, our study presents pioneering and relevant data indicating the potential application of the complex [$Mg(Valp)_2Phen$] as a cytotoxic agent.

Key words: Valproic acid; Magnesium; Glioblastoma multiforme.