

VALIDATION OF AN ANTITUMOR COMPOUND IN 2D AND 3D GLIOBLASTOMA MODELS

Lara González-Rendo,¹ David Moreiras Álvarez,² Martín Baleirón Rodríguez,³ Laura Porres-Ventín,¹ José A. Zumalave,¹ María Isabel Loza García,^{2,3} Víctor M. Arce,¹ José A. Costoya.¹

¹Molecular Oncology Laboratory MOL, Departamento de Fisiología, Centro Singular de Investigación en Medicina Molecular e Enfermedades Crónicas (CiMUS), Universidade de Santiago de Compostela, Instituto de Investigación Sanitaria de Santiago de Compostela (IDIS), Santiago de Compostela, Spain

²Kaertor Foundation, Santiago de Compostela, Spain

³Biofarma Research Group, CiMUS, Universidade de Santiago de Compostela, Spain.

lara.gonzalez.rendo@rai.usc.es

The RB-E2F pathway has a critical role in the control of cell proliferation and, therefore, a valuable therapeutic strategy in cancer could be the decreasing of E2F hyperactivity. Furthermore, the disruption of the PARP1-E2F1 interaction could provide a new therapeutic target for various tumor types, considering that most oncogenic processes are associated with cell cycle dysregulation. With this in mind, we proposed a therapeutic approach focused on the selective inhibition of E2F transcriptional activity in tumor cells. According to preliminary data obtained in our group, PARP1 is a transcriptional co-activator of E2F1 and, because of this, loss of PARP results in restoration of normal cell cycle regulation and reduced tumor growth. To identify compounds that can interfere with this interaction, we obtained a library of 85 compound generated by *in silico* screening of millions of commercially available compounds using the drug discover platform AtomNet (Atomwise). After initial *in vitro* screening, we identified 12 molecules capable of inhibiting this interaction; and the one with better results was selected for further validation using 2D and 3D models of human and murine glioblastoma. For this purpose, we carried out cell viability and migration assays to assess the effect of the compound on two murine and one human glioma cell lines. In all cell lines, cell viability was decreased by treatment. In addition, wound closure response was inhibited in treated cells as compared with controls. Finally, the therapeutic efficacy of this compound was tested in tumoroids originated from those tumor cell lines. In keeping with previous results obtained in 2D cultures, the compound reduced tumoroid growth.

This work was supported by Agencia Estatal de Investigación (AEI/10.13039/501100011033), Xunta de Galicia (GPC GI-1862, ED431B 2020/26; ED431G 2019/02) and European Regional Development Fund-ERDF. AIMS Awards Program – Project A19-513, Atomwise Inc.