***Challenging organic syntheses inspired by naturefrom natural products chemistry to drug discovery***

***COST Action CM1407***

# Meeting dedicated to Early Career Investigators

Brussels, Belgium

18-19 February, 2019

# The potential of c-Src inhibitors Si306 and pro-Si306 for suppressing invasion and overcoming multidrug resistance in glioblastoma

**Marija Stepanović**[a], Ana Podolski-Renić[a], Tijana Stanković[a], Aleksandra Divac Rankov[b], Anna Lucia Fallacara[c], Silvia Schenone[d], Maurizio Botta[c], Milica Pešić[a], Jelena Dinić[a]

[a]*Department of Neurobiology, Institute for Biological Research "Siniša Stanković", University of Belgrade, Belgrade, Serbia*
[b]*Institute of Molecular Genetics and Genetic Engineering, University of Belgrade, Belgrade, Serbia*
[c]*Department of Biotechnology, Chemistry and Pharmacy, University of Siena, Siena, Italy*
[d]*Department of Pharmacy, University of Genoa, Genoa, Italy*

E-mail: marija.stepanovic@ibiss.bg.ac.rs

Glioblastoma multiforme (GBM) are the most frequent and aggressive (WHO grade IV) brain tumors in adults. GBM have high expression of c-Src tyrosine kinase involved in survival, migration and invasiveness of tumor cells. Thus, c-Src emerged as a potential target for GBM therapy.

Cytotoxicity of c-Src inhibitors pyrozolo[3,4-d]pyrimidines, Si306 and its prodrug pro-Si306, was investigated in human GBM cell line U87 and its multidrug resistant (MDR) counterpart U87-TxR by MTT assay. Anti-migratory and anti-invasive effects of Si306 and pro-Si306 were assessed by wound healing, gelatin degradation and transwell invasion assays. The effect of c-Src inhibitors on P-glycoprotein (P-gp) activity in U87-TxR cells was analyzed by flow cytometry. Their ability to reverse paclitaxel resistance in MDR cells was also assessed. Zebrafish model was used to evaluate anti-invasive potential of pro-Si306 on U87 xenografts in vivo.

Novel c-Src inhibitors were significantly more efficient in cell growth inhibition compared to the well-known tyrosine kinase inhibitor dasatinib. The efficacy of Si306 and pro-Si306 was not affected by the MDR phenotype.

Migratory potential of U87 and U87-TxR cells was significantly decreased by both inhibitors. The ability of cells to degrade the matrix and invade through basement membrane was also significantly impaired upon treatment with Si306 and its prodrug. Assessment of intracellular accumulation of fluorescent P-gp substrate showed that both compounds inhibited P-gp activity in U87-TxR cells. Si306 and pro-Si306 also enhanced the paclitaxel efficacy in resistant glioblastoma. In vivo pro-Si306 showed anti-invasive effect against U87 xenografts in zebrafish model.

Considering their ability to suppress migration and invasion and overcome MDR, Si306 and pro-Si306 could be considered in GBM treatment alone or in combination with other chemotherapeutics.