SERBIAN ASSOCIATION FOR CANCER RESEARCH

4TH CONGRESS OF SDIR: BRINGING SCIENCE TO ONCOLOGY PRACTICE: WHERE IS SERBIA?

ABSTRACT BOOK

BELGRADE
3 - 5 OCTOBER
2019

4TH CONGRESS OF THE SERBIAN ASSOCIATION FOR CANCER RESEARCH

WITH INTERNATIONAL PARTICIPATION

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SDIR-4

Belgrade, 3 - 5 October 2019

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SDIR-4
3-5 October 2019, Hotel "M", Bulevar oslobođenja 56a, Belgrade, Serbia

Serbian Association for Cancer Research (SDIR) is a member of the European Association for Cancer Research (EACR).

President of SDIR-4 Congress
dr sc. med. Mirjana Branković-Magić

THE FOURTH CONGRESS OF THE SERBIAN ASSOCIATION FOR CANCER RESEARCH
with international participation "Bringing Science to Oncology Practice: Where is Serbia?"

Belgrade, 3-5 October 2019

Publisher: Srpsko društvo istraživača raka, 11000 Beograd
Year: 2019.
Editors: *dr sc.* Ivana Matić, *dr sc.* Marija Đorđić Crnogorac
Print: DOSIJE STUDIO, Beograd
Number of copies: 120
ISBN: 978-86-919183-2-3

CIP - Каталогизација у публикацији - Народна библиотека Србије, Београд

616-006(048)

SERBIAN Association for Cancer Research. Congress (4 ; 2019 ; Beograd) Bringing Science to Oncology Practice: Where is Serbia? : abstract book / 4th Congress of the Serbian Association for Cancer Research with International Participation SDIR-4, Belgrade, 3 - 5 October 2019 ; [editors Ivana Matić, Marija Đorđić Crnogorac]. - Beograd : Srpsko društvo istraživača raka,, 2019 (Beograd : Dosije studio). - 57 str. ; 23 cm

Tiraž 120. - Registar.

ISBN 978-86-919183-2-3

a) Онкологија - Апстракти

COBISS.SR-ID 279690764

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c-Src inhibitors pyrozolo[3,4-d]pyrimidines, Si306 and pro-Si306, evade multidrug resistant phenotype and suppress invasion in glioblastoma

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Background: 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. **Materials and methods:** Antiproliferative effect of c-Src inhibitors pyrozolo[3,4-d] pyrimidines, Si306 and its prodrug pro-Si306, was assessed in human GBM cell line U87, multidrug resistant (MDR) U87-TxR, and primary GBM cells by MTT assay. Anti-migratory and anti-invasive effects of c-Src inhibitors were evaluated by gelatin degradation and transwell invasion assays. Their effect on c-Src, extracellular signal-related kinase (ERK), and focal adhesion kinase (FAK) expression was analyzed by western-blot and flow-cytometry. Zebrafish model was used to evaluate anti-invasive potential of pro-Si306 in U87 xenografts *in vivo*. **Results and conclusions:** c-Src inhibitors were more efficient in cell growth inhibition compared to dasatinib, a well-known tyrosine kinase inhibitor. The potency of Si306 and pro-Si306 was not affected by the MDR phenotype. Migratory potential of U87, U87-TxR, and primary GBM cells was significantly decreased by both inhibitors. Si306 and pro-Si306 also compromised cells' ability to degrade the matrix and invade through basement membrane. Both compounds reduced phosporylation of c-Src, and its downstream signaling components, ERK and FAK, in GBM cell lines. *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.

Keywords: glioblastoma, multidrug resistance, primary cells, invasion, migration