ДНС Друштво за неуронауке Србије
SNS Serbian Neuroscience Society

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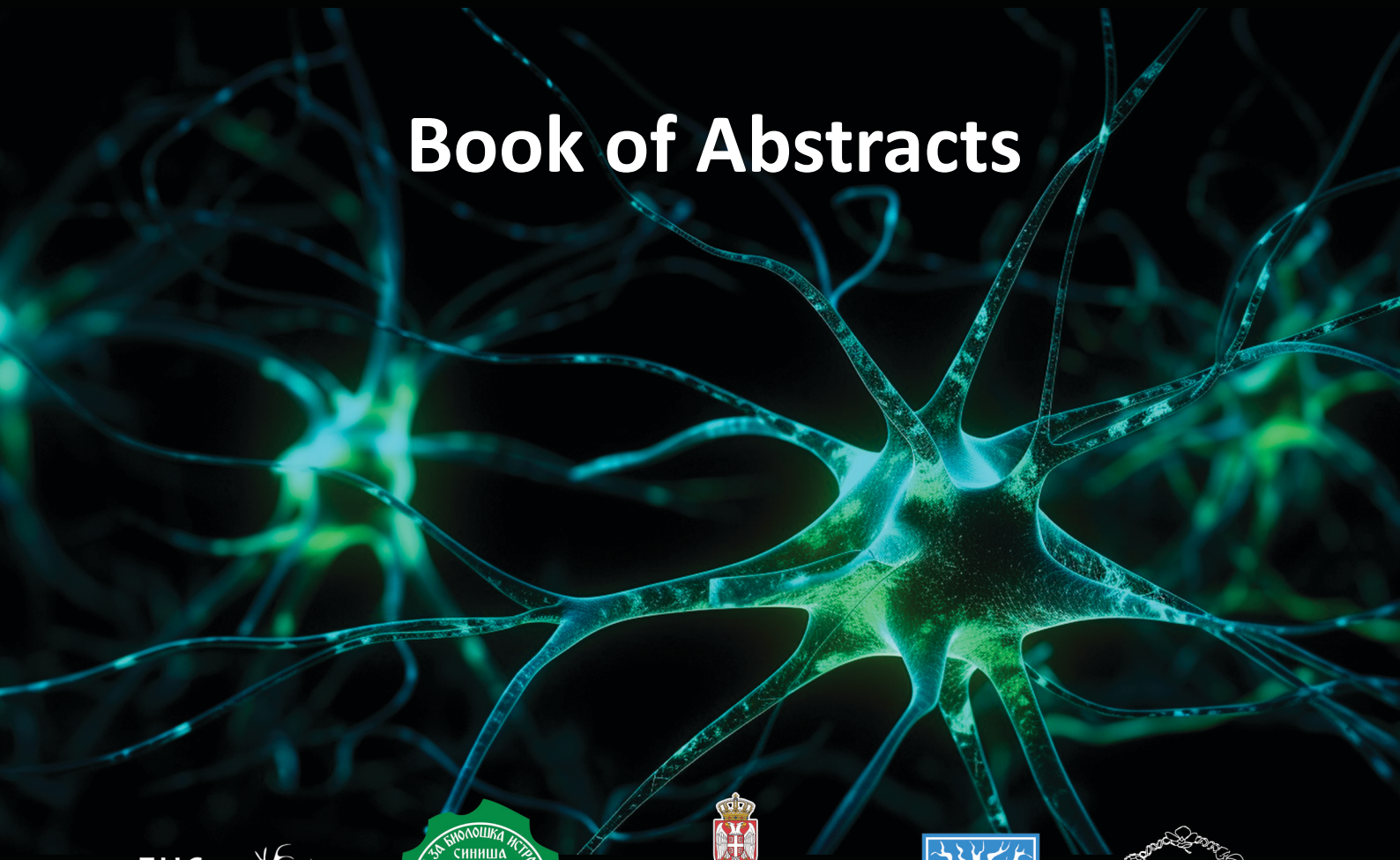
Congress Serbian Neuroscience Society

31 May - 02 June
Belgrade Youth Center
Belgrade



Book of Abstracts

ДНС SNS

Институт за биолошка истраживања Синиша Станковић ИБИСС Универзитет у Београду

Република Србија Министарство науке, технолошког развоја и иновација

Универзитет у Београду Медицински факултет University of Belgrade Faculty of Medicine

Labena

PROMEDIA Laboratory supply specialists

ZEISS

8th CONGRESS OF SERBIAN NEUROSCIENCE SOCIETY with international participation

31 May – 2 June 2023. Belgrade, Serbia - BOOK OF ABSTRACTS

Published by:
Serbian Neuroscience Society
Bulevar despota Stefana 142, 11060 Belgrade, Serbia

Editors
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Anđela Vukojević

Graphic design:
Olga Dubljević, Irina Veselinović

ISBN: 978-86-917255-4-9

The role of the thioredoxin detoxification system in glioblastoma progression and drug resistance

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Glioblastoma (GBM) is the most common and aggressive malignant brain tumor in adults, with an unfavorable prognosis. Only a few chemotherapeutics are used for GBM treatment due to the very low biodistribution of most anticancer drugs in the brain as a consequence of high P-glycoprotein (P-gp) expression in the blood–brain barrier (BBB). However, available GBM treatment remains ineffective due to the high heterogeneity of tumor cells, aggressive invasiveness, and resistance to therapy. Therefore, developing novel therapeutic strategies is of utmost importance. The thioredoxin (Trx) system is an important detoxification system regulating the redox milieu. Components of the Trx system are involved in high-rate proliferation and activation of pro-survival mechanisms in cancer cells, particularly those facing increased oxidative stress. Hence, the Trx system has an important role in tumor progression, as well as in the detoxification and protection of cancer cells from oxidative stress and drug-induced cytotoxicity. Thioredoxin reductase 1 (TrxR1) emerged as a promising target for GBM treatment due to its high expression in GBM. Novel TrxR1 inhibitors – Ugy-type Michael acceptors (UMAs) showed cytotoxic, antiproliferative, and anti-invasive effects in GBM cells, and sensitized GBM cells to temozolomide, a standard chemotherapeutic for GBM treatment. UMA inhibitors induced oxidative stress, mitochondrial depolarization, and elevated expression of antioxidant enzymes in GBM cells. UMA inhibitors suppressed P-gp activity and sensitized resistant GBM cells to paclitaxel. Herein, we showed that investigated TrxR1 inhibitors are promising candidates for GBM that are able to surpass the BBB and overcome drug resistance.