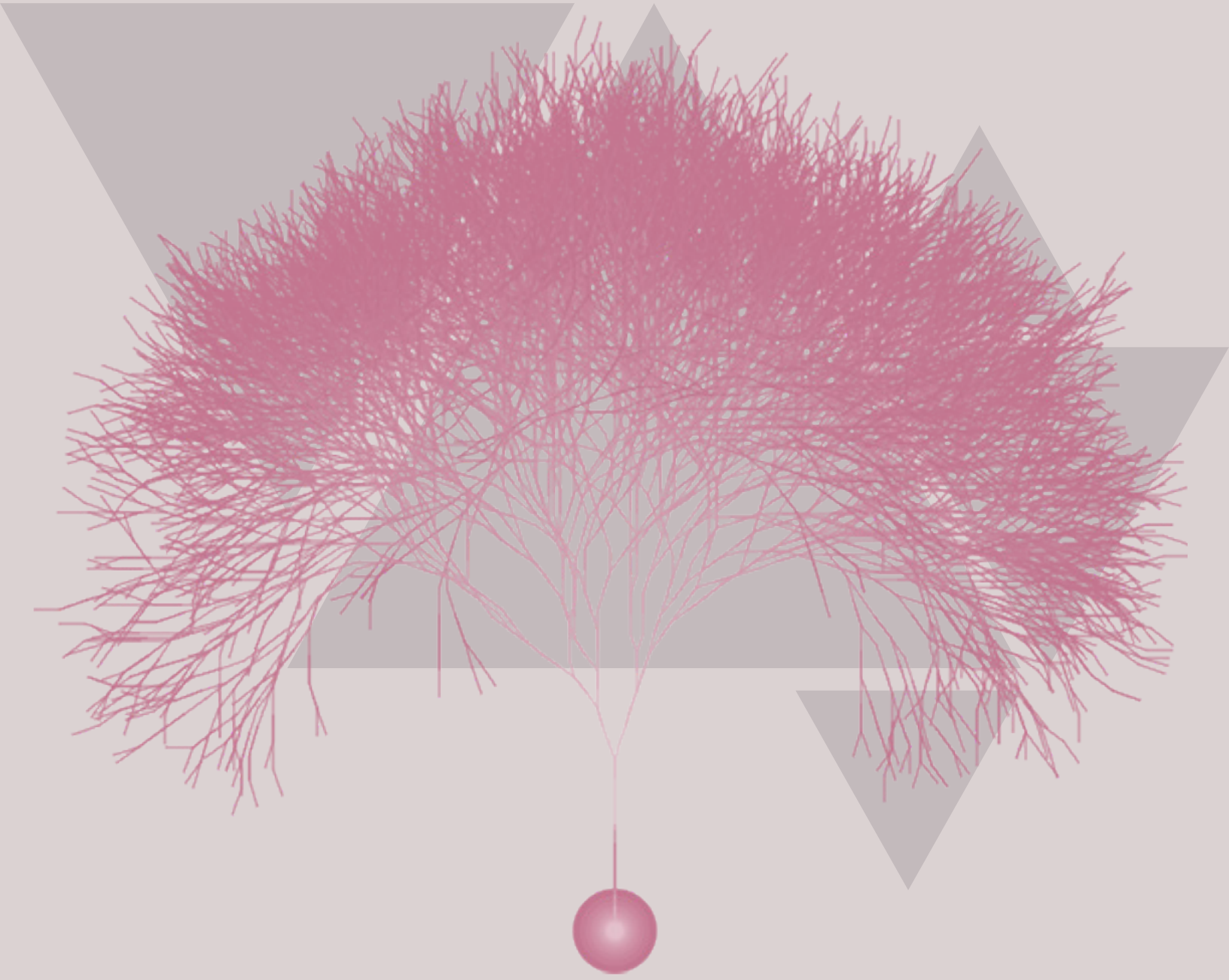
Serbian Society for Mitochondrial and Free Radical Physiology
Third Congress

REDOX MEDICINE

REACTIVE SPECIES SIGNALING, ANALYTICAL METHODS, PHYTOPHARMACY, MOLECULAR MECHANISMS OF DISEASE



Book of Abstracts

Belgrade, September 25-26, 2015.

Serbian society for mitochondrial and free-radical physiology

BOOK OF ABSTRACTS

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SYNERGISTIC ANTICANCER ACTION OF LYSOSOMAL MEMBRANE PERMEABILIZATION AND GLYCOLYSIS INHIBITION

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We investigated the *in vitro* anticancer effect of combining lysosomal membrane permeabilization (LMP)-inducing agent N-dodecylimidazole (NDI) with glycolytic inhibitor 2-deoxy-D-glucose (2DG). Cell viability was measured by MTT and LDH tests. Oxidative stress, lysosomal permeabilization, mitochondrial depolarization and apoptosis/necrosis were analyzed by flow cytometry. Cell morphology was examined by electron microscopy. Intracellular ATP content was measured by bioluminescence assay. NDI-triggered LMP and 2DG-mediated glycolysis block synergized in inducing rapid ATP depletion, mitochondrial damage, and reactive oxygen species (ROS) production, eventually leading to necrotic death of U251 glioma cells, but not primary astrocytes. NDI/2DG-induced death of glioma cells was partly prevented by lysosomal cathepsin inhibitor E64 and antioxidant α-tocopherol, indicating the involvement of LMP and oxidative stress in the observed cytotoxicity. LMP-inducing agents chloroquine and NH_4Cl also displayed synergistic anticancer effect with 2DG, while glycolytic inhibitors iodoacetate and sodium fluoride synergistically cooperated with NDI, thus confirming that the anticancer effect of NDI/2DG combination was indeed due to LMP and glycolysis block, respectively. Based on these results, we propose that NDI-triggered LMP causes initial mitochondrial damage that is further increased by 2DG due to the lack of glycolytic ATP required to maintain mitochondrial health. This leads to a positive feedback cycle of mitochondrial dysfunction, ATP loss, and ROS production, culminating in necrotic cell death. Therefore, the combination of LMP-inducing agents and glycolysis inhibitors seems worthy of further exploration as an anticancer strategy.