STRATAGEM
CA17104

New Diagnostic and Therapeutic Tools against Multidrug Resistant Tumours

ABSTRACT BOOK

STRATAGEM CA17104
Annual Conference
3rd MC meeting and 4th WGs meeting
Belgrade, Serbia
27th - 28th February, 2020

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EUROPEAN COOPERATION IN SCIENCE & TECHNOLOGY

Funded by the Horizon 2020 Framework Programme of the European Union

Welcome to Belgrade

The COST Action CA17104 STRATAGEM Annual Conference – 3rd MC meeting and 4th WGs meetings will take place in Belgrade, at the 88 Rooms Hotel in Belgrade, from 27th to 28th February, 2020. In line with the Action title "New diagnostic and therapeutic tools against multidrug resistant tumours", this meeting will provide an excellent scientific program led by international experts. Invited speakers with different expertize in cancer research, therapy, chemistry, toxicology, and bioinformatics will widen our knowledge from tumor microenvironment to tumor therapy. A talk dedicated to the memory of our honorable colleague Prof. Maurizio Botta will remind us of his work and achievements. His work inspired fruitful collaborations within our COST Action. Besides, special attention will be given to the education of young scientists through the round tables "Meet the invited speakers", "MDR research towards therapy" and "MDR research towards diagnostics". Information on how to apply for the STSM and ITCCG will also be provided during our Annual Conference. ECIs will be given a chance to present their successful STSM stories and compete for the Best Poster Award.
Belgrade – a historic capital full of beauty, history of destruction and reconstruction, famous for its traditional hospitality, food and the best time in Europe – is the perfect place to go for new ideas and collaborations.
We look forward to welcoming you at the STRATAGEM Meeting!

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In silico study to elucidate possible interactions of Hsp90 inhibitors with P-gp

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Heat Shock Protein 90 (Hsp90) is an ATP-dependent molecular chaperone which interacts with a broad range of client proteins involved in cancerogenesis and cancer progression. However, Hsp90 inhibitors were unsuccessful as anticancer agents because of their limitations in physicochemical properties, safety profiles and efflux by membrane transporters responsible for multidrug resistance (MDR) such as P-glycoprotein (P-gp). In the efforts to develop dual targeting molecules with potential to act against both, deregulated cancer metabolism by Hsp90 inhibition and MDR mechanism by P-gp inhibition, eleven Hsp90 inhibitors containing an isoxazolonaphtoquinone core were synthesized and evaluated in sensitive and corresponding resistant cancer cells with P-gp overexpression [1]. Three compounds were identified as dual Hsp90 and P-gp inhibitors. This presentation describes *in silico* studies that were undertaken to elucidate possible interactions of the dual inhibitors with P-gp. In particular, docking simulations were performed using the recently resolved structures of the human P-gp extracted from Protein Data Bank (www.rcsb.org). These structures provide an excellent opportunity for comparison of substrate- and inhibitor-bound structures in the drug-binding cavity of P-gp [2]. Different docking protocols were compared and the one with the best performance on re-docking of the X-ray taxol and zosuquidar structures was selected in terms of: (i) similarity between the generated poses and the corresponding structures in the crystal complex, and (ii) calculated scores, that approximate the binding affinity. The P-gp-ligand interactions were analyzed to outline key residues potentially involved in binding. Based on the results, it was suggested that the binding sites of the studied compounds may partially overlap with a binding site of the P-gp substrate Rhodamine 123, implying that these compounds may act as its competitive inhibitors. The *in silico* results are in accordance with the experimental findings and contribute to the elucidation of the mechanism action of the dual inhibitors.

References

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[2]. Alam A, Kowal J, Broude E, Roninson I, Locher KP (2019) *Science* 363: 753–756.

Acknowledgment: This work was performed within the framework of COST (European Cooperation in Science and Technology) Action CA17104 STRATAGEM—"New diagnostic and therapeutic tools against multidrug resistant tumors". I.T., P.A., T.P. and I.L. acknowledge the financial support from the National Science Fund of Bulgaria, grant number KP-06-COST/3/18.06.2019.