



ABSTRACT BOOK

**COST Action 17104 (STRATAGEM)
WG2 Meeting and International Online
Symposium on “Synthesis and nanodelivery
strategies for new therapeutic tools against
Multidrug Resistant Tumours”**



COST is supported by the EU Framework Programme
Horizon 2020

PROGRAM

9h30 Welcome

9h40 - 13h – MORNING SESSION

9h40 **Keynote Lecture I – Prof. Romano Silvestri (Sapienza University of Rome, Italy):** *New anti-Cancer Agents through an Interaction with Tubulin.*

10h30 **Anne Vessières (Sorbonne Université, France):** *Biological activity of ferrocifens on human PDCLs of glioblastoma (GBMs). A step toward personalized medicine.*

10h50 **Kateřina Valentová (Czech Academy of Sciences, Czech Republic):** *Selectively halogenated flavonoids: Preparation, biophysical properties, and multidrug resistance modulation.*

11h10 **Arasu Ganesan (University of East Anglia, United Kingdom):** *Multitargeting epi-epi drugs for multidrug resistance.*

11h30 **Alfonso T. Garcia-Sosa (University of Tartu, Estonia):** *Predicted Protein Kinase C isoform interactions and experimental inhibition of breast cancer stem cell-inducing spheres.*

11h50 Coffee break

12h - 13h WG2 member meeting (for WG2 members)

13h - 14h – INTERVAL (LUNCH BREAK)

14h - 18h – AFTERNOON SESSION

14h **Keynote Lecture II – Prof. Fabiana Quaglia (Naples University, Italy):** *Biodegradable nanoparticles delivering therapeutic combinations in MDR cancer.*

14h50 **Cristina Del Plato (Istituto Italiano di Tecnologia, Italy):** *Design and synthesis of piperazine-based compounds conjugated to Humanized ferritin as delivery system of siRNA in cancer cells.*

15h10 **Veronica Bastos (University of Aveiro, Portugal):** *UCNPs nanocapsules for doxorubicin targeting delivery in melanoma cell lines.*

15h30 **Denitsa Aluani (Medical University of Sofia, Bulgaria):** *Micellar Encapsulation of Doxorubicin with CAPE Enhance its Cytotoxicity Against Lymphoma L5178 MDR1 cells.*

15h50 **Christina N. Banti (University of Ioannina, Greece):** *Novel silver glycinate metallodrug; A non toxic antiproliferative agent induces apoptosis on human breast cancer cells.*

16h10 Coffee break

16h20 Speed-talks of poster presentations

16h20 **Silvia Cammarone (Sapienza University of Rome, Italy):** *Chalcones and Chalcone-mimetic Derivatives as Notch blocking agents in T-cell acute lymphoblastic leukemia.*

16h25 **Pierre Idlas (University of Angers, France):** *Formulation of ferrocifen loaded lipid nanocapsules against multidrug resistant ovarian adenocarcinoma.*

16h30 **Florence O. McCarthy (University College Cork, Ireland):** *Novel 11-substituted ellipticines as potent anticancer agents with divergent activity against cancer cells.*

- 16h35 **Francesca Picarazzi (University of Siena, Italy):** *Structural elucidation of novel Imidazo[1,2-a]pyridine inhibitors of Aldehyde Dehydrogenase 1A Family.*
- 16h40 **Vera M. S. Isca (Universidade Lusófona de Humanidades e Tecnologias, Lisboa, Portugal):** *Innovative nanosystems with natural cytotoxic royleanone diterpenes from Plectranthus spp.*
- 16h45 **Oscar Briz (University of Salamanca, Spain):** *Transportome manipulation by gene therapy to sensitize liver and gastrointestinal tumors to chemotherapy.*
- 16h50 **Valeria Vergine (Sapienza University of Rome, Italy):** *mPEG_{5kDa}-cholane/Glabrescione B delivery system as promising tool for the treatment of Hh-dependent tumors.*
- 16h55 **Nicolas Clere (University of Angers, France):** *p722 ferrocifen loaded lipid nanocapsules improve survival of murine xenografted-melanoma via a potentiation of apoptosis and an activation of CD8⁺ T lymphocytes.*
- 17h00 **Bruno M. F. Gonçalves (University of Lisbon, Portugal):** *Exploring the efflux and modulation mechanisms of Human ABCG2 through Molecular Dynamics Simulations.*
- 17h05 **Arif Kivrak (Van Yüzüncü Yil University, Turkey):** *Synthesis of Novel Artemisinin-Benzothiophene Hybrid Molecules.*
- 17h10 **Wolfgang Link (Instituto de Investigaciones Biomédicas “Alberto Sols”, Spain):** *Harmine and Piperlongumine revert TRIB2-mediated drug resistance.*
- 17h15 **Mariacristina Failla (University of Turin, Italy):** *NO release regulated by doxorubicin as the green light-harvesting antenna.*
- 17h20 **Sundus Erbas-Cakmak (Konya Food and Agriculture University, Turkey):** *Activatable Photodynamic Therapy Agents for Use in Multi-Drug Resistant Tumors.*
- 17h25 **Enrique Domínguez-Álvarez (Consejo Superior de Investigaciones Científicas, Spain):** *Selenocompounds: a novel approach to fight cancer resistance.*
- 17h30 **Isabella Romeo (Istituto Italiano di Tecnologia, Italy):** *Synergistic inhibition of the Hedgehog pathway by newly designed Smo and Gli antagonists bearing the isoflavone scaffold.*
- 17h35 **David S. P. Cardoso (University of Lisbon, Portugal):** *Generation of a library of indole alkaloid derivatives as ABCB1 inhibitors in resistant cancer cells.*
- 17h40 **Philippe Bertrand (University of Poitiers, France):** *Simplified tetraethylene oxide-mediated synthesis of gold nanoparticles and their internalization by cancer and neuronal cells.*
- 17h45 **Michela Puxeddu (Sapienza University of Rome, Italy):** *New 1,1'-Biphenyl-4-sulfonamides as Potent and Selective Human Carbonic Anhydrase inhibitors.*
- 17h50 **Sarah Le Saux (University of Montpellier, France):** *Stability, cellular interactions and post production modification of murine mesenchymal stem cells (mMSC) derived Extracellular Vesicles.*
- 17h55 **Florence O. McCarthy (University College Cork, Ireland):** *Isoquinolinequinone N-oxides as anticancer agents effective against drug resistant cell lines.*
- 18h00 **Niamh M. O'Boyle (Trinity College Dublin, Ireland):** *Combretazets: Enantiomeric β -Lactams for the Treatment of Breast Cancer.*
- 18h05 **Hulya Ayar Kayali (Izmir Biomedicine and Genome Center, Turkey):** *Synthesis and Characterization of Therapeutic Antibody-drug Conjugates against Multidrug Resistant Ovarian Cancer Therapy.*

18h10 Prizes for best presentations and closing remarks

Multitargeting epi-epi drugs for multidrug resistance

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Epigenetic therapy is now a clinical reality with eight approved drugs that target DNA methyltransferases, histone deacetylases (HDACs) and lysine methyltransferases. A further recent development is the concept of epigenetic multitargeting through the rational design of novel agents that combine the inhibition of an epigenetic pathway with a second non-epigenetic target and five such compounds have advanced to clinical development.

We are investigating the even newer concept of 'epi-epi' drugs that inhibit two separate epigenetic pathways. Such dual targeting agents have the potential to achieve higher efficacy against proliferating cancer cells while reducing tumor resistance. In this presentation, we report a selective dual histone deacetylase and demethylase inhibitor with an IC₅₀ of 0.55 and 0.14 μ M against HDAC6 and LSD1 respectively. The compound was biologically profiled together with control compounds that were either single inhibitors or inactive against either enzyme. The dual inhibitor was active against a panel of leukemia cell lines at a micromolar level and induced apoptosis. Target engagement assays such as CETSA were employed to confirm the inhibition of HDAC6 and LSD1 in cells. Further experiments were carried out to identify synergistic effects with clinically approved agents and promising results were observed with doxorubicin.

References:

- [1]. Ho TCS et al. (2020). *J Med Chem.* 63:12460-12484.
- [2]. de Lera AR and Ganesan A (2020). *Curr Opin Chem Biol.* 57:135-154.
- [3] Liang L et al. (2020). *Bioorg Chem.* 99:103808.
- [4] Lecointre B et al. (2018). *Phil Trans R Soc B.* 373:20170364.