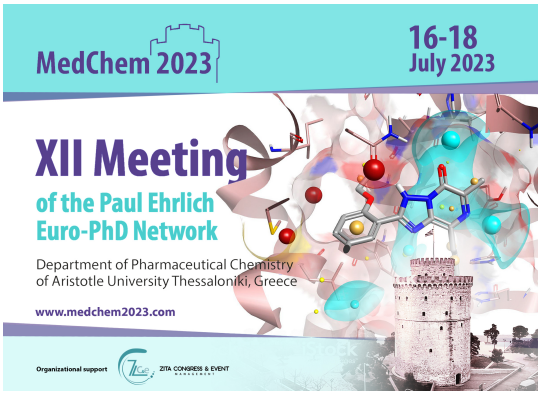

Development of a novel class of YAP:TEAD *interface-3* molecular disruptors to treat colorectal carcinoma

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The transcriptional regulator YAP (Yes-associated protein) is the major downstream effector in the Hippo pathway and is involved in cancer progression and metastases development through the modulation of the activity of hTEAD4 (transcriptional enhanced associate domain) [1]. From a previous repurposing screening, a small in-house library was tested for its cancer cell growth inhibition effect and luciferase-based assay. The p-quinoid IA5 was found to decrease the cytoplasmic level of phosphorylated YAP and the YAP-TEAD complex transcriptional activity and reduce cancer cell growth (HCA46/HT29/HCT116) at micromolar concentrations [2].
Starting from the ChemDiv library, we also have identified two hit compounds (D361 and S049) able to bind at *interface-3* of hTEAD4, the one which is primarily involved in the interaction with YAP. Basing on their scaffolds, the Drug Discovery and Biotechnology Lab has designed and synthesized 40 compounds able to lower total *h*TEAD4 cellular protein levels, and to suppress the transcription of its promoted genes CYR61 (cysteine-rich angiogenic inducer 61) and CTGF (connective tissue growth factor). We are currently implementing an anisotropy fluoresce assay on the recombinant YAP:TEAD complex to test the actual ability of our compounds to disrupt their interaction.
The confirmation of their on-target activity will validate their scaffold, and represents a promising Medicinal Chemistry strategy to fight different subtypes of solid carcinomas.

[1] Santucci M. et al The Hippo Pathway and YAP/TAZ-TEAD Protein-Protein Interaction as Targets for Regenerative Medicine and Cancer Treatment. *J Med Chem.* **2015** Jun 25;58(12):4857-73.

[2] Lauriola A. et al. Identification of a Quinone Derivative as a YAP/TEAD Activity Modulator from a Repurposing Library. *Pharmaceutics*. **2022** Feb 10;14(2):39

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CERTIFICATE

Lorenzo Tagliazucchi

has attended the Paul Ehrlich (PE) Euro-PhD Network from 16th to 18th July 2023

Date
July 20th 2023

Chairman
Prof. Geronikaki Athina