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VABILO NA PREGLOV KOLOKVIJ /
INVITATION TO THE PREGL COLLOQUIUM

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Velika predavalnica Kemijskega inštituta / Lecture Hall, National Institute of Chemistry; Hajdrihova 19, Ljubljana

Targeting Protein-Protein Interactions for Therapeutic Intervention: Challenges and Opportunities

Protein-protein interactions (PPIs) are regulating fundamental processes in living cells and disruption of these essential networks contribute in many human diseases. PPIs represent attractive novel targets for therapeutic intervention and development of small-molecules that modulate PPIs remains a fast growing area in drug discovery field. This presentation will cover the work on two classes of challenging targets: protein-protein interfaces involving long peptide-domain and intrinsically disordered proteins. Myeloid cell leukemia-1 (Mcl-1) is a potent anti-apoptotic protein, member of the prosurvival Bcl-2 family, responsible for regulation of programmed cell death. Overexpression of Mcl-1 is associated with high tumor grade, resistance to chemotherapy and poor prognosis in many types of cancers. It is emerging as a critical survival factor in a broad range of human cancers and represents an attractive molecular target for development of a new class of cancer therapy. Mcl-1 possesses a hydrophobic binding pocket that is capable of binding the BH3-domain of pro-apoptotic Bcl-2 family members. Primarily through these PPIs, Mcl-1 mediates its effects by sequestering pro-apoptotic BH3 containing proteins and inhibiting the programmed cell death. To counter the apoptotic resistance of cancer cells driven by Mcl-1, we have focused on the development of small-molecule mimetics of the BH3 "death" domain to inhibit Mcl-1. Applying high throughput screening approach coupled with computational screening, novel lead compounds were discovered and validated. Further optimization through structure-based design by using HSQC NMR and crystallography studies, potent and selective Mcl-1 small-molecule inhibitors were developed, which bind in the canonical BH3 binding groove. The most potent compounds were biologically characterized with a series of complementary biochemical, functional and cell based assays using model cell lines and established human cancer cells, demonstrating the on-target effect

Vljudno vabljeni / Kindly invited

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