

9th International Conference on

STRUCTURAL BIOLOGY

September 18-20, 2017 Zurich, Switzerland

Type I BIR domain inhibitors in cancer therapy: Designing drugs to modulate the NF- κ B pathway

Federica Cossu

Institute of Biophysics at the National Research Council (IBF-CNR), Italy

Inhibitors of apoptosis proteins (IAPs) constitute a family of conserved proteins whose over-expression enhances cell survival and resistance to anticancer agents. IAPs are E3 ligases, ubiquitylating substrates for the regulation of NF- κ B. Furthermore, they sequester caspases to prevent apoptosis. IAPs interactions occur through type I and type II BIR (Baculovirus IAP repeat) domains. Smac-mimetics (SM) mimicking the active N-terminal peptide of Smac-DIABLO, the natural antagonist of IAPs, have been shown to sensitize cancer cells to apoptosis. SM interact with type II BIR domains of IAPs, thus relieving caspases from X-linked IAP (XIAP) inhibitory activity and leading to cellular IAPs (cIAPs) auto-ubiquitylation and proteasomal degradation within minutes from exposure. Although SM are currently promising candidates for cancer therapy, some cancer cell lines present SM-resistance due to renewed cIAP2 activity and re-activation of NF- κ B. IAPs-mediated regulation of NF- κ B signaling is based on the formation of different protein-protein complexes, regulating ubiquitin-dependent signal transduction cascades. The type I BIR domain from different IAPs has been recognized as a pivotal platform for the assembly of such complexes. We analysed the surface of type I BIR domains (X- and cIAP-BIR1) to identify the hot-spots for the relevant protein-protein interactions. Virtual docking using libraries of compounds returned hits (NF023 and analogues) and can impair BIR1-based complexes with predicted low micromolar affinities that were experimentally confirmed. For this purpose, *in vitro* assays include fluorescence-based and biophysical techniques (thermofluor, microscale thermophoresis, SEC, DLS, SLS). Crystallography on the protein-ligand complexes is the core of the structure-driven approach used for the iterative optimization of specific and selective drug candidates. Treatment of cancer cell cultures with the selected compounds will verify their effects on the modulation of IAPs-dependent signaling cascades. This represents a novel strategy to promote apoptosis in cancer and will unravel new insights on the regulation of NF- κ B pathway.

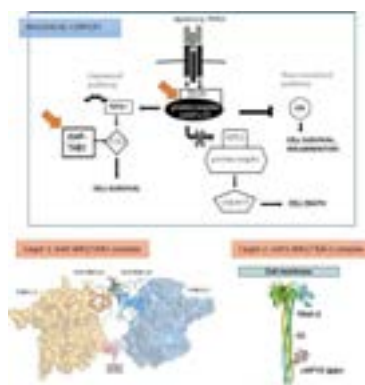


Figure1: Complexes targeted for innovative cancer therapy: Simplified NF- κ B pathway in the upper box: The arrows indicate the protein complexes targeted by our drug design study. Target 1: Crystal structure of XIAP-BIR1 (colored cartoons) in the presence of NF023 (in sticks) superimposed with the crystal structure of BIR1 in complex with TAB1 (colored surfaces, PDB id: 2POP): The compound potentially impairs X-BIR1 dimerization, destabilizing X-BIR1/TAB1 interaction. Target 2: cIAP2-BIR1 is recruited to TRAF2, which is anchored to the TNF receptors. NF023 is shown to impair cIAP2-BIR1/TRAF2 complex *in silico*, with low micromolar affinities

Biography

Federica Cossu has always been interested in the field of cancer research, being fascinated by structural studies of crucial macromolecules and protein complexes involved in the cellular processes of cell death/survival. She gathered experience in cloning, expression, purification and crystallization of recombinant proteins, mainly belonging to the field of cancer. From the last few years, she has focused on the structure-based design of small molecules to be developed, as drug candidates directed to pre-clinical studies. The success of this activity is proved by one patent, one award for her PhD thesis and several publications in the field. She progressively improved her knowledge on biophysical techniques for the study of proteins and on the *in-silico* analysis of protein structures. She has collected experience in European laboratories, including several short visits/experiments at the ESRF synchrotron in Grenoble and at Soleil in Paris. She has been working in lab for ten years, covering various positions within the research group, from Master's degree student to Post-Doctorate. She has been the supervisor of students, also giving lessons on the structural approaches applied to cancer therapy.

federica.cossu@guest.unimi.it