

**P065** Inhibition of DNA double strand repair by trifluoperazine mediates chemosensitization through enhanced activation of stress-induced mitochondrial apoptotic pathway

**Dali Zong, Petra Hååg, Ihor Yakymovych, Leif Stenke, Rolf Lewensohn and Kristina Viktorsson**

*Karolinska Biomics Center, Karolinska Institutet, Stockholm, Sweden*

The cytotoxicity of chemotherapeutic drugs may be augmented by pharmacologic modulation of cellular DNA repair machinery. Here we demonstrate that trifluoperazine (TFP) in combination with bleomycin elicited a strong anti-proliferative response in human non-small cell lung carcinoma (NSCLC) cells, which correlated with significant loss of clonogenic potential. Co-incubation of cells with bleomycin and TFP resulted in higher levels of  $\gamma$ H2AX and persistent autophosphorylation of DNA-PKcs, suggesting perturbations in DSB repair. Consistent with this notion, NSCLC cells treated with the drug combination, but not cells treated with either drug alone, failed to recover from a DNA damage-induced G2 arrest and subsequently underwent cell death with apoptotic morphology, exhibiting massive activation of caspase 3 preceded by Bak/Bax-mediated release of cytochrome c from mitochondria. The role of c-Abl, JNK and BH3-only proteins in the context of TFP-mediated chemosensitization will also be discussed. Taken together, our data is compatible with an inhibition of DSB repair by TFP, which in combination with the DSB-inducing agent bleomycin, leads to a prolonged G2 arrest and subsequent cell demise through mitochondria-mediated apoptosis.