



## President's Poster Abstract

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### **Paclitaxel inhibits osteoclast formation and bone resorption via the modulation of MAPK and G2/M cell cycle arrest**

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Many cancers have a propensity to metastasize to bone, leading to the formation of a vicious cycle of extensive bone destruction and tumor cell expansion. Remedies are critically needed for effective treatment that enables the disruption of this vicious cycle. Paclitaxel has been widely employed for the treatment of several malignant tumours, however, the mechanisms by which paclitaxel influences osteoclast formation, cellular apoptosis and RANKL signaling pathway of MAPKs and NF- $\kappa$ B remains ill-defined. In this study, we demonstrate that low concentrations of paclitaxel (<50 nM) dose dependently inhibited RANKL-induced osteoclastogenesis in both RAW<sub>264.7</sub> cells and bone marrow macrophage cultures. At high concentrations (>50 nM), paclitaxel induced apoptosis in osteoclast-like cells (OLC). Consistent with these findings, OLCs treated with paclitaxel displayed characteristic cytoskeletal aberrations including the disruption of F-actin and microtubule filaments. The inhibition of osteoclastogenesis and onset of apoptosis corresponds with mitotic arrest of the OLCs and their precursors. Pre-treatment of cells with paclitaxel (10 nM, 2 hrs) altered both basal and RANKL-induced activation of NF- $\kappa$ B and mitogen-activated protein kinase (MAPK) signaling molecules p38, ERK and AP-1. Furthermore, we have shown that paclitaxel (5 mg/kg) inhibits Lipopolysaccharide (LPS) induced osteolysis *in vivo* and also inhibits bone resorptive activity of the Giant multinucleated cells that were isolated from patients presenting Giant cell tumour of bone. Given its dual anti-cancer and anti-osteoclastogenic properties, paclitaxel may offer unique benefits for the treatment of cancers concomitant with osteolytic conditions.