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Akt is a mediator of *in vivo* derived cisplatin resistance in isogenically paired ovarian cancer cell lines

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Ovarian cancer is characterised by a typically advanced stage at presentation and the development of resistance to current chemotherapy. These features largely account for the poor prognosis associated with this disease.

Platinum based compounds are the most effective for treating ovarian cancer and regimens including a platinum agent are the cornerstone of ovarian cancer chemotherapy. Several mechanisms including altered DNA repair pathways and defective apoptotic responses have been implicated in platinum resistance.

We are using isogenically paired cell line models, derived from the ascites of individual ovarian cancer patients before and after the onset of platinum resistance, to identify clinically relevant determinants of resistance.

Recently, we identified Akt as a key modulator of resistance to cisplatin in these clinically derived cell line models. Treatment of sensitive cells with cisplatin results in an activation of caspase-3 which is attenuated in the resistant lines. Caspase-3 activation by cisplatin is enhanced by pretreatment of cells with the Akt inhibitor API-2. This increase appears to be modest in the sensitive cells but is striking in the resistant lines and is accompanied by rapid detachment of the cells; a phenotype not seen on treatment with API-2 or cisplatin alone.

We have also shown that siRNA knockdown of Akt-1, -2 and -3 isoforms can recapitulate the effect of API-2 treatment on these cells and will present data relating to the effect of API-2 treatment in a series of clear cell carcinoma lines: a rare histological sub-type of ovarian cancer characterised by an inherent resistance to platinum.