Enhancement of cisplatin action due to combination with bortezomib in ovarian *in vitro* tumour models

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Although widely used in the clinic [1], cisplatin has two major limitations namely (1) limited spectrum of activity due to intrinsic and/or acquired resistance and (2) the toxic side-effects including nausea, vomiting, nephrotoxicity, ototoxicity, neurotoxicity, and peripheral neuropathy [2]. Hence there is need for newer and better drugs and more effective mode of treatment. Cisplatin, being a neutral compound, can cross the cell membrane by passive diffusion. It is also found to it enter the cell by carrier-mediated transport such as that involving the copper transporter1, CTR1 [3, 4]. However, cisplatin triggers the down-regulation and proteasomal degradation of CTR1 in human ovarian cancer. Bortezomib, a proteasome inhibitor approved for treatment against relapsed multiple myeloma, has been reported to block cisplatin-induced down-regulation of CTR1 [5]. Thus, it is logical to assume that in the presence of bortezomib the cellular uptake of cisplatin may be increased which in turn may result into increased platinum-DNA binding and ultimately pronounced apoptosis. In other words, cisplatin and bortezomib in combination may act synergistically. In this project we are investigating synergism from sequenced combination of cisplatin with bortezomib in the human ovarian tumor models. The results of the study including drug potency, synergism from sequenced combination of cisplatin and bortezomib will be presented in the poster.

References:
[1] Stordal B, Davey M. Understanding cisplatin resistance using cellular models. *IUBMB Life* (2007), 59(11), 696-639.
[2] Hoskins, W.J., Perez, C.A., and Young, R.C. (2005) *Principles and practice of gynecologic oncology*. Fourth edition. Philadelphia. Lippincott Williams and Wilkins.
[3] Safaei, R., Role of copper transporters in the uptake and efflux of platinum containing drugs. *Cancer letters* 234 (2006), 34-39.
[4] Binks, S.P., Dobrota, M. Kinetics and mechanism of uptake of platinum-based pharmaceuticals by the rat small intestine, *Biochem. Pharmacol*. 40 (1990) 1329-1336.
[5] Jandial, D.D., *et al.,* Enhanced Delivery of Cisplatin to Intraperitoneal Ovarian Carcinomas Mediated by the Effects of Bortezomib on the Human Copper Transporter 1, *Clin Cancer Res*, 15n (2009), 553-560.