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Lobaplatin – A third-generation platinum agent with high in vitro efficacy across a wide range of cancer cells

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Platinum-based chemotherapy plays an important role in the management of solid tumors since more than 30 years. Thousands of new platinum analogues have been synthesized since the discovery of cisplatin to overcome adverse effects, induction of resistance and limitations in clinical activity. But only three compounds (cisplatin, carboplatin, oxaliplatin) have a world wide approval for the treatment of cancers. Platinum drugs are used as single compounds or in combination with other chemotherapeutic agents in many standard therapeutic regimens.
The present study was designed to explore the *in vitro* activity of lobaplatin against a wide range of human tumor cell lines including resistant subtypes. Results from proliferation experiments under various conditions and the effects on the cell cycle of tumor cells are presented together with data from apoptosis assays.
In comparison to other platinum derivatives which are in clinical use or in development (cisplatin, oxaliplatin, nedaplatin, satraplatin, and carboplatin) we have found that lobaplatin expresses a high activity on tumor cell lines of different origin. In the XTT proliferation assay lobaplatin exhibits IC_{50} values from 0.3 μM to 61 μM (mean IC_{50} 19.4 μM) against 24 tumor cell lines, together with a maximum of growth inhibition between 78% and 100% (mean 85.2%). The efficacy of lobaplatin is much higher than the activity of cisplatin, nedaplatin, and carboplatin. No cross-resistance to cisplatin could be observed on cisplatin resistant cell line A2780cis. In addition lobaplatin retains activity against multi-drug resistant cell lines with P-gp1 and MRP1 overexpression in comparison to their sensitive wild types.
Flow cytometric analysis demonstrates that treatment of KB/HeLa cells with lobaplatin affects the cells in a time and concentration dependent manner. Treatment with high doses of lobaplatin (10 μM) leads to a considerable enrichment of cells in S-phase after 24h and up to 120h. Cells treated with low doses of lobaplatin (3.16 and 1 μM) showed a delayed G2/M arrest after 48h with an increase of apoptotic cell population for at least 120h. The results are underlined by cell count experiments designed to distinguish effects on cell viability and on cell proliferation.
The new results corroborate that lobaplatin has excellent *in vitro* activity against various cancer cell lines, and support the further clinical development of the candidate in phase II trials. Lobaplatin is already on the market in China.

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D-501036, a novel selenophene-base triheterocycle derivative, exhibits potent in vitro and in vivo anti-tumoral activity, which involves DNA-damage and ATM activation

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Background: D-501036, 2,5-bis(5-hydroxymethyl-2-selenienyl)-3-hydroxy-methyl-N-methylpyrrole, a novel selenophene derivative, was identified in our laboratory as a novel antineoplastic agent. In this study, we examined the *in vitro* and *in vivo* anticancer efficacy, and explored the mechanism of action of this compound in human cancer cells.
Materials and Methods: The *in vitro* and *in vivo* anticancer effect of D-501036 was examined by the MTS assay and human xenograft model. DNA gel eletrophoresis, flow cytometry, ICP-MS, and Western blotting were used to reveal molecular events in this study.
Results: D-501036 exhibited a broad spectrum of antitumor activity against many human cancer cells with GI_{50} in nanomolar range. However, very low toxicity was found to the primary culture of kidney, lung and fibroblast. No cross-resistance with D-501036 was observed in KB-Taxol, vincristine, or CPT-resistant derivative cell lines. Significant S phase arrest followed by sub-G_1 population accumulation after cancer cells exposed to D-501036. DNA fragmentation and caspase-3 activation further indicated that D-501036 induced cell death through an apoptotic pathway. Furthermore, rapid activation of p53, p21 and ATM signaling pathway and *en masse* DNA damage were found in D-501036-treated cancer cells. However, our results demonstrated that D-501036 did not intercalate into chromosome nor inhibit the topoisomerase I/II enzyme activity, indicates that D-501036-induced DNA-damage is unlikely through the change of DNA topology. Significant amount of ROS production was found shortly after cancer cells exposed to D-501036, but partial reverse D-501036 cytotoxicity by pretreated with antioxidant. Furthermore, large amount of DNA-adduct in the D-501036-treated tumor cells by ICP-mass were found.
Conclusions: Taken together, these results suggested that the tumor growth inhibition function of D-501036 might contribute by the induction of ROS and DNA-adduct formation. Intraperitoneally administrated of D-501036 to Ncr nude/nude mice resulted a complete abrogate the growth of xenografted human renal carcinoma cells. Based on the striking antitumor efficacy of this substance, we believed the potential for this polyselenophene compound becomes to an efficacious anticancer drug is remarkably promising.

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Phase I trial of the histone deacetylase inhibitor valproic acid with the topoisomerase I inhibitor, karenitecin in advanced melanoma

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Background: Metastatic melanoma is a devastating disease currently lacking effective treatment. We have previously shown that the novel topo I inhibitor, karenitecin, can produce clinical benefit in 34% of patients with advanced melanoma. In melanoma cell lines, we have shown that pretreatment with the histone deacetylase inhibitor (HDACi), valproic acid (VPA), can increase binding of topo I poisons to DNA, potentiate apoptosis and produce synergistic cytotoxicity. Similar results were obtained in the A375 melanoma xenograft model with synergistic suppression of tumor growth. Based on this data we hypothesized that sequential VPA followed by karenitecin could produce enhanced clinical response without augmenting bone marrow suppression, which is the major toxicity of karenitecin.
Methods and Study Design: The *primary objective* was to determine the toxicity and maximum tolerated dose (MTD) of VPA given orally twice daily for 5 days sequentially with karenitecin given I.V. daily for 5 days every 3 weeks. The *secondary objectives* were to determine the pharmacokinetic parameters of VPA and karenitecin in combination. Patient had adequate organ function, ECOG PS 0–1 and progressive disease on at least 1 systemic therapy.
Results: Twenty-five patients have been enrolled to date. VPA doses of 30 mg/kg/day, 45 mg/kg/day and 60 mg/kg/day for five days were well tolerated when combined with karenitecin at 0.8 mg/m^2/day for five days. Karenitecin dose was therefore escalated to 1 mg/m^2/day for five days and this could be combined with VPA at 60 mg/kg/day for five days. No DLT was observed. Doses were escalated to VPA 90 mg/kg/day and at this level 2/3 patients experienced neuron-vestibular DLT. Subsequently, VPA was de-escalated to 75 mg/kg/day and this proved tolerable. PK for valproic acid and karenitecin are described in this combination. Histone acetylation in PBMC was examined and shows a linear increase with dose.
Conclusion: This phase I trial demonstrates that the HDACi VPA can be combined at an effective dose with full doses of the topo I inhibitor karenitecin. Encouraging clinical responses (prolonged stable disease and minor responses) have been seen in this heavily pretreated patient population at all VPA dose levels. A Phase II trial ith this combination in melanoma is currently ongoing.

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A novel HPLC/MS assay to measure DNA interstrand cross-linking efficacy in oligonucleotides of varying sequence

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Until now the main method of evaluating the DNA interstrand cross-linking ability of cancer chemotherapeutic agents (in terms of both DNA binding affinity and sequence selectivity) has involved the electrophoresis of radiolabelled oligonucleotides on denaturing gels after incubation with an agent. To avoid the use of radioactivity we have developed a method based on ion-pair RPLC/mass spectrometry which allows characterization and quantitation of drug–DNA interstrand cross-links formed within short oligonucleotides. The other advantage of this assay is that all species separated by the chromatographic process can be identified by mass spectrometry. Using this methodology we have investigated the rate and sequence-selectivity of the DNA interaction of SJG-136 (SG2000), a pyrrolobenzodiazepine (PBD) dimer currently being evaluated in Phase I clinical trials in the UK and USA. The interaction of SJG-136 was