Conclusion: IT-101 is found to have a favorable safety and PK profile in humans, confirming the intended properties of its nanoparticle formulation design. Observations of prolonged stable disease in multiple patients with advanced solid tumors demonstrate biological activity and support further clinical development.

424 POSTER

Development of novel cancer cell-selective cell-penetrating peptides for the advanced peptide-based drug delivery system

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Background: Recently, the cell-penetrating peptides (CPP) have gained great attention as a carrier which enable to introduce various proteins and siRNAs in vitro and in vivo. One of the most important advantage is "non-invasiveness" of the oligopeptides to the cells and tissues in vivo. Among these, TAT and pAnt (antennapedia) are the most representative CPPs, however, they unselectively penetrate to cells with various origins. Here we report the highly efficient novel CPPs showing cancer cell-selective cell penetrating feature (named "CCS-CPPs") which were isolated from the artificial random peptide library.
Materials and Methods: Over forty novel CPPs which encode the different 15 amino acid sequences were isolated from the unique random peptide library at an initial step, then examined their tumor cell-selective penetration using a panel of human tumor cell lines with different origins including carcinomas, sarcomas, brain tumors and hematopoitic malignancies as a second screening.
Results: Based on the tumor cell penetrating assay, we identified over ten different novel CCS-CPPs which shows high permeability to human cancers with different origins such as colon adenocarcinomas, breast carcinomas, lung adenocarcinomas and hepatocellular carcinomas. Moreover, we also found CPPs selectively penetrate into sarcomas or hematopoietic malignancies. Noticeably, all these tumor specific CPPs generally showed lower incorporation into non-neoplastic cells such as fibroblast and peripheral blood lymphocytes, and also the permeability of these CCS-CPPs were prominently superior to that of the TAT peptide.
Conclusions: These novel CCS-CPPs are considered to be quite useful as a novel peptide-based delivery tool to construct the advanced cancer cell-targeted molecular therapies.

425 POSTER

Significantly enhanced therapeutic profile of docetaxel in novel nanopharmaceutical CRLX288

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Background: Docetaxel is a chemotherapeutic agent used broadly across multiple tumor types with over $3B in annual sales. Dose-limiting myelosuppressive toxicities are associated with high maximum concentration (C_{max}) systemic drug exposure resulting from intravenous injection. Clinical experience of weekly dosing with lower dose levels has mitigated some toxicity, but compromised efficacy compared to a conventional every-3-week high dose regimen. We set out to enhance the efficacy of docetaxel by increasing drug localization to the tumor and mitigating docetaxel C_{max}-driven toxicity with a novel polymeric nanoparticle formulation.
Material and Methods: CRLX288 was developed with our proprietary PEGylated polymeric nanoparticle technology (PNP), by conjugating docetaxel to the biodegradable polymer poly (lactic-co-glycolic acid) and forming nanoparticles by nanoprecipitation. CRLX288 has been optimized for particle size, surface potential, and particle surface properties to achieve favorable pharmacokinetics and to maximize efficacy. The same chemical and physical properties have also been optimized to minimize immunogenicity and reduce systemic clearance by the reticuloendothelial system. CRLX288 was evaluated for both tumor growth delay and pharmacokinetics in a range of tumor-bearing mouse models via intravenous administration.
Results: Mouse pharmacokinetic and biodistribution data demonstrate that CRLX288 has prolonged circulation time and enhanced tumor localization compared to the parent drug docetaxel, as evidenced by both half-life and Area Under the Curve values. Such improved pharmacokinetics is correlated with enhanced drug retention in tumor tissues. Results from tumor growth delay studies of CRLX288 also illustrate that our PNP technology confers a higher maximum-tolerated dose, dramatically superior efficacy, and longer dosing interval compared to the parent drug docetaxel. Confocal microscopy confirms that the improved efficacy and tolerability of CRLX288 nanopharmaceutical formulation is mediated by enhanced tumor penetration, and intracellular uptake and release of the parent drug in tumor cells, resulting in prolonged and sustained drug exposure.
Conclusions: Taken together, our findings on CRLX288 illustrates PNP is a powerful nanopharmaceutical technology platform capable of maximizing the therapeutic value of a broadly used pharmaceutical product, creating potentially unprecedented therapeutic opportunities for patients.

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Phase I study of oral CP-4126, a gemcitabine analog, in patients with advanced solid tumours

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Background: CP-4126 (gemcitabine-5′-elaidic acid ester) is a novel nucleoside analogue with preclinical antitumoral activity. CP-4126 has been solubilised in a lipid-based formulation and encapsulated in non-gelatine hard shell capsules. The purpose of this dose-escalating study was to assess safety, the pharmacokinetics (PK), and preliminary antitumor activity of the oral formulation and determine the recommended dose (RD) for phase II.
Methods: Patients with advanced refractory solid tumours, performance status ECOG $\leqslant$2, adequate haematologic, renal and hepatic function were enrolled. The study had a two-step design; a non-randomised dose-escalating step I with oral CP-4126 alone, followed by a randomised, cross-over step II comparing oral CP-4126 with IV gemcitabine (gem). In step I CP-4126 was given on days (d) 1, 8, 15 q4w in increasing doses until MTD and RD are established. Serial blood samples were collected for PK analysis on d1 in step I.
Results: 26 (m = 8; f = 18) patients (45−80 years age range) were enrolled in step I at 7 dose levels (100–3000 mg/day), and received 1 to 6 treatment cycles. The major indications were pancreatic, colon or breast cancer. Most frequent AEs were fatigue and AST/ALT increases, the majority being grade 1−2. One DLT was reported at 1300 mg/day after two doses of CP-4126: γGT grade 4, and ALT/AST and fatigue grade 3. All together, 10 patients experienced disease stabilisation according to RECIST evaluation, where the best response was a 25% reduction from baseline (vaginal cancer). CP-4126 was not detected in plasma at doses up to 1300 mg of CP-4126 and only trace amounts appeared at higher dose levels. dFdC concentrations (C_{max}) and exposure (AUC) increased linearly with CP-4126 dose, indicating that oral CP-4126 acts as a prodrug for gemcitabine. The enrolment of patients was terminated in Stage I at the 3000 mg dose level due to relative poor bioavailability of dFdC. The RD was not established.
Conclusions: Oral CP-4126 is a prodrug for gemcitabine in humans. It is well tolerated at doses up to 3000 mg/day in a d1,8,15 q4w schedule and the safety profile is very good. An early efficacy signal compared with gemcitabine historical data was reported. However, due to a low bioavailability of dFdC the study was stopped at a dose-level of 3000 mg/day in Stage I without determination of the RD.

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The development and evaluation of an experimental model for assessing convective fluid flow through multicell layers

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Introduction: One of the consequences of elevated interstitial fluid pressure (IFP) in solid tumours is that the normal process of convective fluid flow through tissues is impeded. Therapeutic strategies designed to overcome 'pharmacokinetic' resistance by re-establishing convective fluid flow are of interest but these studies are constrained by the requirement for in vivo models. The aim of this study was to develop an in vitro model that could be used to measure convective fluid flow and to assess the impact convective fluid flow has on drug penetration through multicell layers.
Methods: The model consists of a transwell cell culture insert which supports the growth of multicell layers on collagen coated membranes with a pore size of 3 microns. A graduated tube is inserted into the transwell