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

E. Kondo[1]. [1]*Aichi Cancer Center Research Institute, Division of Oncological Pathology, Nagoya, Japan*

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

S. Eliasof[1], P.S. Ng[1], P. Lim Soo[1], J. Podobinski[1], R.I. Case[1], P. Shum[1], J.G. Martinez[1], S.R. Kabir[1], D. Lazarus[1], S. Svenson[1]. [1]*Cerulean Pharma Inc., Research & Development, Cambridge, USA*

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.

426 POSTER

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

F.E. Stuurman[1], E.E. Voest[2], A. Awada[3], J.H.M. Schellens[1], P.O. Witteveen[2], T. Bergeland[4], P.A. Hals[4], A. Hendlisz[3]. [1]*Netherlands Cancer Institute − Antoni van Leeuwenhoek Hospital, Clinical Pharmacology, Amsterdam, The Netherlands;* [2]*University Medical Center Utrecht (UMCU), Medical Oncology, Utrecht, The Netherlands;* [3]*Jules Bordet Institute, Medical Oncology, Brussels, Belgium;* [4]*Clavis Pharma ASA,Oslo, Norway*

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.

427 POSTER

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

R. Phillips[1], H. Makeen[1], N. Periasamy[1], P. Loadman[1], S. Smye[2], B. Sleeman[3], P. Jones[4], C. Evans[5], C. Twelves[6]. [1]*University of Bradford, Institute of Cancer Therapeutics, Bradford, United Kingdom;* [2]*University of Leeds, Department of Medical Physics and Engineering, Leeds, United Kingdom;* [3]*University of Leeds, Department of Applied Mathematics, Leeds, United Kingdom;* [4]*Leeds Institute of Molecular Medicine, Section of Molecular Gastroenterology, Leeds, United Kingdom;* [5]*University of Leeds, Division of Medical Physics, Leeds, United Kingdom;* [6]*Leeds Institute of Molecular Medicine, Section of Oncology and Clinical Research, Leeds, United Kingdom*

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

apparatus and a pressure gradient is applied across the membrane by raising the fluid level in the tube above that of the bottom chamber. Convective fluid flow is determined by weighing the medium in the bottom chamber as a function of time. Doxorubicin was added to the top chamber and its ability to cross the multicell layer was determined by HPLC in the presence and absence of a pressure gradient.
Results: Using a physiologically relevant pressure gradient of 28.8 mmHg, convective fluid flow progressively decreased as the thickness of the multicell layer increased. DLD-1 multicell layers with a thickness of 47.6±11.2 microns completely impeded convective fluid flow (<0.01 ml/min). Using a multicell layer of 12.9±3.0 microns and a pressure gradient of 28.8 mmHg, convective fluid flow was 0.192 ml/min. Under these conditions, the rate of penetration of doxorubicin across the multicell layer was 75 fold greater than when no pressure gradient exists.
Conclusions: This study demonstrates that the absence of convective fluid flow significantly reduces drug penetration through multicell layers. By increasing the thickness of the multicell layer and blocking convective fluid flow, this system provides an experimental model for evaluating strategies designed to re-establish convective fluid flow by targeting cell:cell or cell:matrix interactions.

428 POSTER

Targeting delivery systems mediated by a novel peptide for breast cancer therapy and imaging

H.C. Wu[1], M.S. Chen[1], C.Y. Chiu[1]. [1]*Academia Sinica, Institute of Cellular and Organismic Biology, Taipei, Taiwan*

Anticancer drugs lack selective toxicity leads to their dose-limiting side effects which compromise clinical outcome. Targeting liposomes that bind to surface receptors of cancer cells is a recognized strategy for improving the therapeutic effectiveness of conventional chemotherapeutics. In this study, we isolated several ligands from a phage-displayed peptide library that bind to breast cancer cells. Targeting peptides were found to bind to breast cancer cells *in vitro* and breast cancer xenografts *in vivo*. The targeting peptide-linked liposomes were capable of translocating across the plasma membrane into endosomes through receptor-mediated endocytosis. Targeting peptides also recognized the tumor tissue in surgical specimens of breast cancer patients, with a positive rate of 90%. The tumor site fluorescent intensity in the mice treated with targeting peptide-linked quantum dots (QD) was around 28-fold of that in the mice treated with QD. When the targeting peptides were coupled to liposomes carrying doxorubicin, the therapeutic index against breast cancer xenografts was markedly enhanced. We conclude that the targeting peptides may be used to improve the systemic chemotherapy of breast cancer or to diagnose this malignancy.

429 POSTER

Design and development of nanocarrier for efficient drug delivery into the brain

A. Orthmann[1], R. Zeisig[2], I. Fichtner[1]. [1]*Max-Delbrueck-Center for Molecular Medicine, Experimental Pharmacology, Berlin, Germany;* [2]*EPO GmbH, Experimental Pharmacology and Ocology, Berlin, Germany*

The success in the treatment of brain cancer or brain metastases by chemotherapy is very limited because of the efficient blood–brain barrier (BBB) which prevents most drugs from reaching tumour cells in the brain. An encapsulation of cytostatic drugs into liposomal nanocarrier may help to overcome the tight cell layer of the BBB and to enhance the therapeutic effect.
The aim of the study was to develop Trojan Horse Liposomes (THL) for an improved drug transport of anticancer drugs across the BBB to enhance the anti-tumour effect. In a first part we optimized the membrane properties of vesicles with respect to a better passive uptake by and transport through a tight cell barrier *in vitro*. In the second part, the most efficient liposomes were surface modified for an active targeting using a 19-mer peptide sequence (Angiopep) to increase specific uptake and transcellular transport. It was already shown that Angiopep passes the BBB by a physiological transcytosis process mediated by the low density lipoprotein receptor related protein (LRP) receptors expressed on the surface of the BBB and brain cancer cells.
In this study we could demonstrate *in vitro* that the liposomal nanocarrier with an optimised composition of the lipid membrane (L2) and the Angiopep ligand, bound to the liposomal surface, significantly improved cellular uptake by epithelial (MDCK II), endothelial (bEnd.3) and glioama (U373) cells. Transcytosis through a tight cell barrier using the MDCK II model demonstrated that the highest amount of calcein passed through the cell layer was induced by the THL-L2 formulation.
In vivo studies using a human xenograft brain metastasis model (MT-3 breast cancer) in nude mice showed already a significantly better anti-tumour effect of Mitoxantrone loaded L2-liposomes compared to the free drug. In addition, clearly fewer side effects like gastrointestinal complications, weight loss and dehydration were observed.
The therapeutic effect was further improved if THL-L2 liposomes were used, resulting in an additional tumour volume reduction as compared to L2.
Our results demonstrate that the obstacle in the chemotherapeutic treatment of brain tumours and metastases in the brain can be overcome by liposomal nanocarrier with carefully composed bilayer and surface modification with the Angiopep sequence to obtain an improved transport through the BBB.

Natural products, new cytotoxics, clinical trials

430 POSTER

Dose finding of inecalcitol, a new VDR agonist, in combination with docetaxel–prednisone regimen for castrate-resistant prostate cancer (HRPC) patients (pts)

J. Medioni[1], G. Deplanque[2], J.M. Ferrero[3], T. Maurina[4], J.M. Rodier[5], E. Raymond[5], G. Allyon[1], S. Renaux[6], J.F. Dufour-Lamartinie[6], S. Oudard[1]. [1]*Hôpital Européen Georges Pompidou, Oncology, Paris, France;* [2]*Centre Hospitalier St Joseph, Oncology, Paris, France;* [3]*Centre Antoine Lacassagne, Oncology, Nice, France;* [4]*Centre Hospitalier Universitaire Jean Mimoz, Oncology, Besançon, France;* [5]*Hôpital Beaujon, Oncology, Clichy, France;* [6]*Hybrigenics, Clinical Rd, Paris, France*

Introduction: Inecalcitol is a novel Vitamin D Receptor (VDR) agonist which shows high antiproliferative effects in human cancer cell lines and a 100-fold lower hypercalcemic activity than calcitriol the natural ligand of VDR.
Methods: In this study, escalating dosages of inecalcitol were combined to chemotherapy in chemonaive CRPC patients. Safety and efficacy were evaluated in groups of 3−6 patients receiving inecalcitol every other day (qod), once a day (qd) or twice a day (bid) on a 21-day cycle in combination with docetaxel (75 mg/m^2 q3w) and oral prednisone (5 mg bid). Biphosphonates were prohibited during the first cycle. Patients received up to six cycles unless unacceptable toxicity or disease progression. Primary endpoint was Dose Limiting Toxicity (DLT) defined as grade 3 hypercalcemia within the first cycle. Calcemia, creatininemia and CBC were assessed weekly; biochemistry, ECG and PSA every 3 weeks. Efficacy endpoint was PSA response defined as ⩾30% decline within 3 months.
Results: Eight dose levels from 40 to 8000 μg have been evaluated in 54 pts; 83 % had bone metastases, 12% had visceral disease only. Median age was 71 years [range, 49−87], median Gleason score (Gs) 7 [42% Gs 10−8, 58% Gs 7−6] and median PSA 31.7 ng/mL [range, 0.8–962.4]. 5 patients had PSA level <2ng/mL.
Up to the daily dose of 4000 μg no significant changes in calcemia have been observed. Only hypercalcemia grade1 of short duration occurred in 24% of patients.
DLT (hypercalcemia G3) occurred in 2 out of 4 patients receiving 8000 μg/day (4000 μg bid). DLT was observed after 1 week and 2 weeks of treatment respectively. In both cases, calcemia normalized in few days after interruption of treatment. The 2 other patients treated at this dose level experienced hypercalcemia G2 and were switched to 4000 μg qd.
The Maximum Tolerated Dose (MTD) is defined at 4000 μg qd since none of the patients treated at this dose level experienced hypercalcemia > G1 even after more than 3 cycles of treatment. Blood levels of inecalcitol reached antiproliferative concentrations without inducing hypercalcemia.
Most of the adverse events (AES) reported were grade 2 except hematological toxicities which were not increased or decreased with the addition of inecalcitol. Asthenia (48%), constipation (33%), diarrhea (31%), nausea (17%), headache (12%), vomiting (7%), mucitis/mucositis (7%), anorexia (7%), fever (7%) were the most frequent AEs. None was considered related to inecalcitol. Frequency of AEs related to docetaxel did not seem to be modified.
Efficacy analyses have been performed on 47 pts treated up to the dose of 2000 μg. PSA responses with this combination are encouraging. 83% of the treated patients had ⩾30% PSA decline within 3 months of treatment since in historical data around 65% are responder with docetaxel as a single agent. Moreover, 50% PSA decline was observed in 67% of pts and time to biochemical relapse was 169 days.
Conclusion: High antiproliferative daily dose of inecalcitol, a new VDR, agonist has been safely used in combination with docetaxel in HRPC patients. This combination treatment shows encouraging PSA response with 83% of responder. A multicenter randomized double blind Phase 3 study is forecasted to confirm these results.