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Poster Highlights I

Peter Robins

Address
Current Drugs Ltd
Middlesex House
34-42 Cleveland Street
London
W1P 6LB
UK
Email: peterro@cursci.co.uk

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A-176120

Among the new drugs presented in the morning poster session on the first day of the AACR meeting was Abbott Laboratories' A-176120, an analog of farnesyl pyrophosphate and an inhibitor of Ras farnesyltransferase (FTase). The compound was discovered as part of an SAR program at Abbott to develop antihypercholesterolemic inhibitors of squalene synthase (SSase) without activity at FTase. Certain 1,2-analogs of a series of cyclobutanes, such as A-87049, showed acceptable selectivity profiles, but this was reversed in 1,3-analogs, eg, A-87050, which were potent inhibitors of FTase, but weak inhibitors of SSase. When the alkyl groups of A-87050 were replaced with benzyl (eg, A-88681), SSase activity was virtually eliminated. Replacement of the cyclobutane moiety with benzene-1,2,4,5-tetracarboxylic acid led to A-122330 which was even more potent. Final modifications then led to A-176120, which showed IC_{50} = 1.18 ± 0.3 nM for FTase (compared to 10,000 nM for SSase) and was selective over the closely-related enzymes, geranylgeranyltransferase I and II (IC_{50} = 423 and 3000 nM, respectively). A-176120 also inhibited Ras processing in NIH3T3 H-Ras transformed cells and HCT116 K-Ras mutated cells with ED_{50} = 1.6 and 0.5 µM, respectively.

3-IAABU

Another poster described the cancericidal effects of the tubulin ligand, 3-(iodoacetamido)benzoylurea (3-IAABU), which has almost completed preclinical trials and is being prepared for phase I clinical trials by Mount Sinai School of Medicine, New York and the Kaplan Cancer Center, in collaboration with Pharmacia & Upjohn Inc. 3-IAABU was discovered via a screening program with Cytoskeleton Inc of Denver, Colorado, USA, and has shown activity in a range of cancer cell lines with ID_{90} values in the range 0.015 to 0.29 µM for leukemic cells and 0.06 to 0.92 µM for solid tumor cells. 3-IAABU also inhibits the growth of Daudi cells with or without expression of P-glycoprotein (Pgp), suggesting that it is not a substrate for Pgp and is therefore independent of MDR-related drug resistance.

TAS-102

5-Fluorothymidine (FTD) is effective against human tumors that are resistant to 5-FU, but is metabolized by thymidine phosphorylase (TPase) to the inactive metabolite, 5-fluorothymine. Taiho Pharmaceutical Co Ltd has developed TAS-102, a nucleoside-based antitumor therapy consisting of FTD and the TPase inhibitor (TPI), 5-chloro-6-(2-iminopyrrolidin-1-yl)methyl-2,4(1H,3H)pyrimidinedione hydrochloride, in a 1:0.5 ratio, which effectively prevents the biological functions of thymidine phosphorylase, such as angiogenesis and metastasis. Given the role of FTD as a substrate for TPase, the preclinical pharmacokinetics (PK) of TAS-102 were of prime importance and species differences in the PK profiles were presented in a poster from Taisho. The monkey was exceptionally different from rat and dog, showing a higher concentration of FTD in the plasma and a slower elimination time. Since the inhibition rate of TPase digestion of FTD by TPI in human tissues was similar to that of monkey tissues, it is expected that TAS-102 will be effective in the clinical setting and the compound has now entered phase I clinical trials.

PNU-214936

Tumor-targeting Staphylococcal enterotoxin A (SEA)-Fab fusion proteins are potent T-cell activators which are being investigated by Pharmacia & Upjohn for breast and lung cancers. The first-generation SEA-fusion protein, PNU-214565 (r-C242Fab-SEA), reached phase I clinical trials but was discontinued due to systemic toxicities, such as fever and hypotension, at low doses. Toxicity was inversely correlated to baseline concentrations of plasma anti-SEA, which are unpredictable and widely variable. Development was superseded by a second-generation fusion protein, PNU-214936 (Fab5T4V13-SEAm9), which has a mutation at residue 227 of SEA that disrupts the MHC class II intermediate affinity zinc-bridge binding site and improves its therapeutic window. PNU-214936 may thus be administered at doses up to 32-fold greater than those used with PNU-214565. The new phase I clinical trial is designed so that no pair of individuals with equivalent baseline levels of anti-SEA will receive the same dose of drug.

TAS-106

A series of five posters from Taiho Pharmaceutical Co Ltd described the preclinical pharmacology and toxicology of the new TAS-106, a novel antitumor ribonucleoside, for which the major cytotoxic mechanism appears to be inhibition of RNA synthesis. The IC_{50} values of cell growth in culture were 0.033 and 0.035 µM, following exposure for 24 and 72 h, respectively. Moreover, almost the same IC_{50} (0.068 µM) was obtained when cells were exposed to drug for 4 h on each of 3 days. The *in vivo* antitumor activity of TAS-106 was assessed against human tumor xenografts in nude rats on three different dosage schedules in a 2-week dosing system. The doses selected were the minimum toxic doses on each of the schedules: 6 mg/kg/day once a week, 1 mg/kg/day 3 times a week, and 0.3 mg/kg/day 5 times a week. The tumor growth inhibition rates (IRs) of TAS-106 for OCUM-2MD3 stomach tumors on the once a week, 3 times a week, and 5 times a week schedules were 91.8, 89.2 and 90.8%, respectively, while the IRs for LX-1 lung tumors were 98.0, 90.6 and 83.5%, respectively. Schedule-independent antitumor efficacy was suggested to be a pharmacological characteristic of TAS-106, which is expected to begin clinical trials in the US in September.

CHS-828

Leo Pharmaceutical Products Ltd is developing the novel cytotoxic antitumor agent, CHS-828 (N-[6-(4-chlorophenoxy)hexyl]-N'-cyano-N"-4-pyridylguanidine), which was selected via a screening program based on human and rodent tumor cell lines. CHS-828 showed a different activity profile in ten different cell lines from known alkylating agents, topoisomerase inhibitors, antimetabolites and spindle poisons. Oral treatment with CHS-828 in non-toxic doses caused tumor growth arrest (100 mg/kg once daily) or tumor regression (250 mg/kg once weekly) in MCF-7 tumor bearing mice. Mice with NYH small cell lung cancer xenografts were particularly sensitive to CHS-828, with a total regression of tumors at 30 mg/kg once daily. Disease-free survival was observed after 4 weeks treatment with 250 mg/kg once weekly. Toxicity associated with high-dose CHS-828 consisted mainly of gastrointestinal disturbances and atrophy of lymphoid organs. CHS-828 is at present undergoing phase I clinical evaluation in three patients in Uppsala, in collaboration with the European Organization for Treatment of Cancer. Although the lowest dose is still being investigated, early indications are that the drug is well tolerated.

PNU-166196

Pharmacia & Upjohn Inc is developing PNU-166196, a new α-bromoacryloyl derivative of distamycin A. It is a member of a novel class of DNA minor groove binders which displays potent cytotoxic activity *in vitro* on human and murine tumor cell lines and antitumor activity *in vivo* against experimental tumor models showing an outstandingly high therapeutic index. Pharmacia plans to begin phase I clinical trials with this compound in October or November 1999.

CDDO

From a series of some 200 analogs of oleannane triterpenoids, researchers at Dartmouth Medical School, NH, USA, have selected a nitrile derivative, 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid (CDDO), which shows promise as a chemopreventive agent. In particular, it effectively inhibits many leukemia cell lines at concentrations ranging from 0.001 to 1 μM. *In vitro* work with LCDB leukemia cells is being carried out by J Letterio (National Cancer Institute, USA) who presented a separate poster that described the ability of the compound to induce cell differentiation. *In vivo* work with the compound is scheduled to start shortly, with a view to preparing the compound ultimately for human trials in myeloid leukemia.

CCI-779

The sirolimus analog CCI-779 (or cell cycle inhibitor 779) was described in a poster from Wyeth-Ayerst Research. This has a very similar profile to rapamycin but has been developed as a superior iv formulation. Growth inhibitory effects were blocked by the FKBP inhibitory molecule ascomycin, suggesting that the mechanism of action of CCI-779 is similar to sirolimus. PDGF stimulation of the human glioblastoma line T98G was markedly inhibited (IC_{50} ~ 1 pM) by CCI-779 in serum free medium. In nude mouse xenografts, the growth of staged human glioblastoma (U87MG) tumors was blocked by a variety of dosing regimens, with a minimum effective dose of 0.1 to 1.0 mg/kg. Staged tumors treated for 5 consecutive days with CCI-779 were still growth inhibited 14 days later. In contrast, the effect of the compound on immune function was lost as early as 1 day after drug withdrawal. Various histological tumor types (pancreas, breast, prostate) were also sensitive to CCI-779 in nude mouse xenografts. These data suggest that CCI-779 will be an effective antitumor agent for several human tumor types when given via an intermittent dosing regimen; the compound began phase I clinical trials at two sites in Europe and the US in the last quarter of 1998.

NSC-609395 and NSC-639829

SRI International of Menlo Park, CA, USA, presented a pair of posters describing preclinical toxicology studies with a pair of NCI compounds, halichondrin B (NSC-609395) and NSC-639829 (dimethylaminobenzoylphenylurea). The former is a structurally-unique tubulin-binding compound derived from extracts of Pacific sponge of the genus, *Axinella* which was cytotoxic *in vivo* in the murine P-388, B16 and L1210 models, and showed activity in preliminary data from *in vivo* models of human melanoma, colon and ovarian solid tumor xenografts. However, development of the compound was terminated due to undisclosed problems, although work continues at the NCI to discover structural analogs that might prove more suitable. NSC-639829, on the other hand, has proceeded well through preclinical evaluation and work related to an IND application that is expected to be filed before the end of the year has begun.

CEP-701

Pancreatic ductal adenocarcinoma (PDAC) is highly refractory to available treatment regimens and associated with a poor survival rate. Cephalon Inc is developing a number of Trk tyrosine kinase inhibitors, including CEP-701 (Figure 1), which have shown excellent promise for the treatment of this disease. CEP-701 is selective for this enzyme and demonstrated the following IC_{50} values in preclinical assays of conventional protein tryosine kinase inhibitors: 2 nM (Trk); 65 nM (VEGFR); >10,000 nM (InsR); >10,000 nM (EGFR); and 43 nM (PKC). CEP-701 (100 nM) potently inhibits Trk in intact cells (75 to 100%) and inhibited PDGFR by up to 100% in intact cells. CEP-751, the O-methyl derivative of CEP-701, was in fact the lead compound from this program and an iv prodrug formulation completed phase I clinical trials, but its development has been put on hold as a result of particularly positive results from phase I trials of CEP-701. An oral formulation of the latter compound has now completed phase I trials in normal volunteers. Phase II trials in prostate cancer are expected to begin in the US before the end of 1999, and will include an arm in pancreas cancer in gemcitabine-treated and -naive patients.

Onconase

Alfacell Corp is developing Onconase, a novel amphibian ribonuclease with a broad-spectrum of antitumor activity that is currently in phase III trials for malignant mesothelioma. Based on previously observed *in vitro* synergisms between Onconase and doxorubicin (DOX) against MDA-MB-231 breast cancer cells, the company conducted studies with Onconase and DOX as single agents and in combination in two *in vivo* models in nude mice: a flank model (tumor cells administered sc); and a systemic lung metastatic and survival model (tumor cells administered iv). In both flank and systemic models, Onconase

was used at 2.5 mg/kg dose ip twice a week for 3 weeks, and DOX at 3 or 5 mg/kg on the same schedule iv. Systemic treatments started 3 days after tumor inoculation. The combination had a significantly greater effect than either agent alone, resulting in a decrease of tumor size (flank) and number of metastatic foci (systemic). It also had a significantly greater effect on prolongation of survival time, with median survival times of 58, 72, 76 and 187 days for control, Onconase, DOX (5 mg/kg) and Onconase + DOX (5 mg/kg), respectively. The increased life span for the last group was 222%, of which 30% were long-term survivors. In the ongoing study, the beneficial effect of the combination of ONC+DOX on survival in mice has been confirmed with a lower dose of DOX (3 mg/kg). Onconase has already been tested as a single agent in a preliminary, broad-eligibility phase II trial involving 17 patients with breast cancer, and demonstrated highly favorable results that the company ultimately hopes to use as a basis for phase III trials, although it is concentrating resources on the phase III trials in mesothelioma.

A-177430

The matrix metalloproteinase (MMP) family is implicated in the progression of several malignancies including prostate cancer. A poster from Abbott Laboratories described the ability of a new macrocyclic MMP inhibitor, A-177430, to block tumor growth and metastases in a syngeneic model of rat prostate cancer. A-177430 is highly potent in substrate assays *in vitro* against a number of different MMPs, including fibroblast collagenase (MMP-1; IC_{50} = 1.8 nM); gelatinase-A (MMP-2; IC_{50} = 2.2 nM); gelatinase-B (MMP-9; IC_{50} = 5.6 nM); stromelysin (MMP-3; IC_{50} = 3.9 nM) and matrilysin (MMP-2; IC_{50} = 1.6 nM). In *in vivo* studies, male Copenhagen rats were inoculated with Mat Ly Lu rat prostate cancer cells (1 x 10(6) cells sc) and administered A-177430 (10 to 100 mg/kg/day ip) for 16 days. The compound produced a dose-dependent decrease in tumor volume compared to control, most significantly in the lungs, where no evidence of metastatic tumor metastases was observed after treatment with the maximum dose.

NSC-691236 and NSC-691237

A pair of posters from the National Cancer Institute (NCI) described the pharmacokinetics and toxicity in cynomolgus monkeys of two Pseudomonas exotoxin monoclonal antibody conjugates. LMB-9 (B3ds(Fv)-PE38; NSC-691236) is a disulfide-stabilized form of LMB-7, a single chain immunotoxin cytotoxic to Le_y antigen-bearing tumor cells, while BL22 (RFB4 ds(Fv)-PE38; NSC-691237) is toxic for CD22+ cells and exhibits antitumor activity in nude mice bearing human B-cell lymphomas. LMB-9 was eliminated biexponentially from plasma with a half-life of 86 to 94 minutes; peak plasma levels were 0.61 and 7.69 µg/ml in monkeys treated with 0.1 mg/kg or 1.0 mg/kg, respectively. Leukocytosis occurred in all dose groups and one animal showed marked gastric ulceration and slight renal tubular necrosis upon histopathological examination. Administration of the second antibody conjugate, BL22 (0, 0.1, 1.0, 1.25, 1.75, and 2.0 mg/kg iv qd every other day) produced lethargy and non dose-related leukocytosis in all dose groups. No significant changes were noted in the percentage of mononuclear cell populations positive for CD20 or CD22. Elevated heart rate and mean arterial pressure occurred at 2.0 mg/kg/dose. Plasma levels ranged from 2.5 to 53 µg/ml (0.1 to 2.0 mg/kg/dose) 10 minutes post-dose. It is hoped that both LMB-9 and BL22 will enter clinical trials at some point, although it is not clear when this might occur.

TSP-1 analogs

Taffy Williams, President and CEO of InKine Pharmaceuticals Co Inc (PA, USA), presented a poster describing the antimetastatic activity of thrombospondin type 1 (TSP-1) repeat peptides, Cys-Ser-Val-Thr-Cys-Gly, and their analogs in both *in vitro* and *in vivo* assays. These peptides inhibited TSP-1-dependent *in vitro* tumor cell adhesion and invasion in a dose-range of 50 to 300 µg/ml, while experimental melanoma tumor cell metastasis was inhibited by 50 to 90% in mice treated with peptide in a dose range of 0.01 to 1.0 mg/mouse administered either iv or ip. Scrambled peptide controls had no effect. Inhibition of metastasis was detected immediately after tumor implantation and 24 to 72 h later, suggesting that the peptide not only blocks initial tumor arrest but also subsequent tumor development. An undisclosed lead peptide has been identified, which will shortly undergo toxicological studies; it is expected to enter phase I clinical trials before the end of 1999. The work has also led to the identification of compounds potentially useful as imaging agents, these too are expected to commence clinical trials in 1999, although corporate partners are being sought for this aspect of the program.

Tomatoes

While virtually all other foodstuffs seem to have their 15 minutes as potential carcinogens, new medical research suggests that the consumption of tomatoes, or more specifically lycopene, the carotenoid that gives them their colour, may actually prevent some forms of cancer. The Barbara Ann Karmanos Cancer Institute presented results from a study in prostate cancer patients with Lyc-O-Mato, a formulation of lycopene from Lycored Natural Products Ind Ltd in Beer-Sheva, Israel. A total of 21 men with localized prostate cancer, scheduled for radical prostatectomy were randomly assigned to receive either Lyc-O-Mato (15 mg po bid) or no intervention for three weeks prior to surgery. Serum and tissue lycopene levels increased significantly in the intervention group, while levels of prostate-specific antigen declined significantly over three weeks in the same group. Within the treated group, 8 of 12 patients (67%) had organ-confined prostate cancer and 84% had tumors ≤ 4 cm^3, compared to 44% and 55%, respectively, in the control group. The expression of biomarkers of proliferation decreased, whereas the markers of differentiation and apoptosis increased in the intervention group.

MR1(scFv)

A single-chain antibody fragment, MR1(scFv), with specific binding to tumor-associated EGFRvIII has been developed by Duke University Medical Center in collaboration with the Ottawa Regional Cancer Centre and the National Cancer Institute (NCI). A poster described work with [^{125}I]-radiolabeled MR1(scFv) which has been used to demonstrate specific and high-level targeting of xenografts. The affinity KA of MR1(scFv) for EGFRvIII by BIAcore analysis was 4.3 x 10^7 M, and by Scatchard analysis was 1.0 x 10^8 M. Specificity of MR1(scFv) for EGFRvIII was demonstrated *in vitro* by incubating radiolabeled MR1 (scFv) with the U87MG. ΔEGFR cell line in the presence or absence of competing unlabeled MR1(scFv). In biodistribution studies using athymic mice bearing sc U87MG ΔEGFR tumor

xenografts, animals received paired-label intratumoral infusions of [^{125}I]SIPC-MR1(scFv) and [^{131}I]SIPC-anti-Tac(scFv) as a control. MR1(scFv) demonstrated a high tumor uptake of 85% (1 h) and 16% (24 h) injected dose/g following administration. Specific/control scFv tumor uptake ratios of more than 20:1 demonstrated specific localization of MR1(scFv). The excellent tumor retention of MR1(scFv) combined with its rapid clearance from normal tissues results in high tumor-to-normal organ ratios. It is hoped that the antibody fragment, or a similar example, will enter phase I clinical trials by the end of 1999.

R-101933

A series of four posters from Janssen Pharmaceutica NV described the ability of a new, oral, imidazo-benzazepine P-glycoprotein (Pgp) antagonist, R-101933 (Figure 1) to modulate multidrug resistance (MDR) without altering the pharmacokinetics of a co-administered drug. R-101933 concentration-dependently restored the antiproliferative effect of anthracyclines, taxanes and vinca alkaloids in Pgp-overexpressing K562 human leukemia cells, while demonstrating complete reversal of the sensitivity level of the non-resistant, Pgp-negative K562 cells at 3 mM. Complete reversal of the uptake and restoration of the intracellular distribution of daunorubicin to the nucleus was also observed with R-101933 or S-9788 (10 mM; Servier) but not with verapamil. R-101933 appears to act not as a Pgp substrate but rather a Pgp antagonist. Furthermore, in photoaffinity labeling experiments with [^{3}H]azidopine, R-101933 inhibited Pgp labeling with IC_{50} = 0.84 μM, making it over hundred-fold more active than verapamil (IC_{50} = 110 μM). Oral treatment with R-101933 restores the sensitivity towards paclitaxel and adriamycin in resistant human tumors xenografted in athymic mice. Phase I trials of the compound began in The Netherlands in 1998, in which the compound has shown no significant alteration of the pharmacokinetics or pharmacodynamis of paclitaxel or docetaxel in patients.

T-138067

Tularik Inc has discovered and optimized a novel class of cytotoxic pentafluorobenzenesulfonamides with efficacy against cell lines that express the MDR phenotype. These new agents are active against a broad variety of cell lines from breast, colon, ovarian, renal, lung, CNS and prostate tumors, and melanoma; for instance, the lead compound, T-138067 (Figure 1), demonstrates the following IC_{50} values (μM): 0.05 (MCF-7); 0.034 (CCRF-CEM); 0.025 (DC-3F); and, 0.06 (P388). A poster from the company described the SAR leading to this compound, which is currently undergoing phase I clinical trials that have yet to reach the maximum tolerated dose. Electron donating groups in the 4-position of aryl substituents on the sulfonamide were optimal for potency. Small alkoxy substituents were preferred, with maximum activity observed with methoxy. Aniline-derived sulfonamides were also preferred, compared to those derived from benzylamine or phenethylamine, while inversion of the sulfonamide resulted in effectively complete loss of activity. Secondary sulfonamides were optimal.

TER-286

Telik Inc is investigating the tumor-associated glutathione-S-transferase isotype P1-1 (GSTP1-1) as the target for a number of potential anticancer treatments. A pair of posters at this conference reported work with the GSTP1-1 inhibitor, TER-199 (Figure 1), and its de-esterified analog, TER-117, which are effective inhibitors of MRP-1-mediated drug resistance. The program with GSTP1-1 has led to TER-286, a novel nitrogen mustard prodrug which was reported in a separate poster. This is not an inhibitor of GSTP1-1, but requires activation by the enzyme so employs a quite different strategy from TER-199 and analogs. In mouse embryo fibroblasts made from wild-type (wt) and *GSTP1-1* knockout mice, the latter exhibited 2-fold greater resistance to TER-286 compared to the wt (96.0 ± 20.0 μM compared to 177.5 ± 42.0 μM). Thus tumors expressing high levels of GSTP1-1 will be more sensitive to the cytotoxic effect of the drug. The drug has been selected as the first clinical candidate from the program and is scheduled to begin phase I clinical trials at the beginning of 2000.

Figure 1.