concentration-dependent manner without receptor level alteration. Proliferation assays using HER1-, HER2- and non-overexpressing human breast carcinoma cells revealed that treatment with either D-69491 or D-70166 inhibited cell growth to similar extent. Independent of HER1 and HER2 expression levels, D-70166 inhibited proliferation of the human breast carcinoma cells MDA-MB-468, MDA-MB-453, SK-BR-3, MDA-MB-231 and MCF-7 with IC_{50} concentrations ranging between 0,86 and 2,85 μM and average maximal growth inhibition of 79% to control cells. This suggests that in addition to HER2- and HER1-driven cell growth inhibition, D-70166 exhibited unspecific cytotoxicity. Whereas the growth inhibitory effects of D-69491 on SK-BR-3, MDA-MB-453 and MDA-MB-231 cells were comparable to the effects observed after D-70166 treatment, D-69491 achieved lower inhibitory responses on MCF-7 cells and higher responses on HER1-overexpressing MDA-MB-468. Our *in vitro* data demonstrated that both D-70166 and D-69491 are potential clinical candidates, which target EGFR as well as HER2 tyrosine kinase activities.

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The potential role of STI 571 in the treatment of head and neck cancer

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The complete response of head and neck cancer to systemic therapies is often disappointing. The novel agent STI 571 (2-phenyl aminopyrimidine derivative) is designed to be effective against CML via inhibition of Bcr-Abl kinase. However the drug is known to inhibit other tyrosine kinases, including PDGFR and c-kit. There is evidence that c-kit is expressed in certain head and neck tumours including 90% of adenoid cystic carcinomas (ACC). The aim of this study is to provide pre-clinical data on the response of a panel of head and neck squamous cell carcinoma (SCC) cell lines along with primary explanted tumour cell cultures (adenoid cystic and SCC) to STI 571. We have also explored the interaction of STI 571 when given in combination with commonly used chemotherapuetic agents.. STI 571 alone shows significant growth inhibition against in both SCC cell lines and primary cultures. In SCC cell lines STI 571 was also found to be synergistic with several agents and antagonistic with gemcitabine. These Gemcytabine results were mirrored in ACC primary cultures, and a degree of synergy with other drugs was also observed. The growth inhibitory effect of STI 571 in ACC can be explained by inhibition of the c-kit receptor kinase expressed in these tumours. However this cannot explain the toxicity seen in c-kit –ve SCC cell cultures. It is proposed that this effect is mediated via an as yet unidentified kinase pathway. Likewise the reported synergy and antagonism may well be due to inhibition of other kinases. Studies are ongoing to further establish the role of these kinases in the toxicity of STI571. Furthermore work is ongoing to explore the possible role of STI571 in the treatment of c-kit +ve ACC's, both as a single agent and in combination. Clinical studies are planned to follow this.

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Cellular responses to DNA topoisomerase I poisons and the TOR kinase inhibitor, rapamycin

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Genetic analyses of cellular responses to DNA topoisomerase I (Top1) poisons in the budding yeast Saccharomyces cerevisiae suggest common pathways regulate the cytotoxicity of rapamycin, a Tor kinase inhibitor. Eukaryotic topoisomerase I plays an important role in DNA replication and recombination. Camptothecin (CPT) targets the enzyme by reversibly stabilizing a covalent Top1-DNA intermediate. During S-phase, these complexes are converted into irreversible DNA lesions as a consequence of collisions with advancing replication forks. To define cellular factors that recognize or repair Top1-induced lesions, conditional tah mutants were isolated with enhanced sensitivity to top1T722A at 35oC. The self-poisoning top1T722A mutant is a CPT mimetic that avoids issues of drug transport. Nine TAH genes (including CDC45, DPB11, DOA4, TAH11 and SLA1) were identified that protect cells from top1T722A-induced DNA damage. These mutants were hypersensitive to hydroxyurea and exhibited terminal phenotypes consistent with S-phase induced DNA lesions. Remarkably, the majority of tah mutants were also hypersensitive to rapamycin. This macrocyclic antibiotic targets the PI3-related TOR kinase (mTOR in mammalian cells, Tor1 and Tor2 in yeast) and induces cell cycle arrest in G1 phase. Yeast and mammalian Tor kinases regulate protein translation and cell cycle progression in response to growth signals and nutrient deprivation. Rapamycin has demonstrated surprising antitumor activity in clinical trials, consistent with recent reports of rapamycin-induced apoptosis observed in p53 null cells. The enhanced sensitivity of yeast tah mutants to CPT and rapamycin suggest specific alterations in S-phase potentiate the cytotoxicity of both agents. The ability of extragenic repressors of doa4-10 to suppress top1T722A- or rapamycin-induced lethality provides further support for similar mechanisms of drug action, which may be investigated in yeast. Supported by NIH grants CA23099, CA58755, CA77776 and ALSAC.

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A phase I study of ZD 1839 (Iressa) in combination with oxaliplatin, 5-fluorouracil (5-FU) and leucovorin (LV) in advanced solid malignancies

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Iressa is an oral small molecule tyrosine kinase inhibitor of the epidermal growth factor receptor (EGFR-TKI). Preclinical studies demonstrated promising anti-tumor effects using Iressa alone or in combination with chemotherapy agents in a variety of epithelial tumors. We report the results of a phase I dose-escalation study that investigates the tolerability and clinical biology of Iressa in combination with oxaliplatin, and 5-FU/LV. A sequential dose escalation of Iressa and oxaliplatin was performed. From July 2001 to April 2002, 16 patients (10 men: 6 women, median age 50.5 years, range 31-61 years) were treated. The median number of prior chemotherapy regimens was 1.5 (range 0-3). Twelve patients had stage IV adenocarcinoma of the colon, 1 patient an adenocarcinoma of unknown primary, 1 patient a squamous cell carcinoma of unknown primary, and 1 patient a basosquamous cell carcinoma of unknown primary. Three dose levels were tested. A total of 102 cycles were administered (range 1-8). A dose-limiting toxicity was seen at the second dose level (catheter-related bacteremia). One patient at the third dose level experienced a DLT with grade 3 nausea, diarrhea, and hypokalemia requiring hospitalization for intravenous hydration. This dose level (Iressa 500 mg daily, with a standard dose and a every two week schedule of oxaliplatin, 5-FU/LV) established the phase II recommended dose (MTDs) for Iressa and oxaliplatin combined with 5-FU/LV. Additional grade 3/4 toxicities were neutropenia without fever (4). Grade 2 toxicities consisted of acneiform rash (6), vomiting (5), abdominal pain (4), diarrhea (4), nausea (3), fatigue (2), mucositis (2), thrombocytopenia (2), anemia (1), anorexia (1), and personality/behavioral change (1). Grade 1 toxicities included nausea (11), sensory neuropathy (8), fatigue (7), vomiting (7), anorexia (6), diarrhea (6), abdominal pain (1), ALT elevation (1), AST elevation (1), and fever (1). Three patients with colorectal cancer had a partial response. Nine patients had stable disease after a minimum of 4 cycles of treatment. Pharmacokinetic and biological endpoint studies are ongoing. Currently, a phase II study of this regimen in colorectal cancer is in progress and these results will be presented.

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Antitumor activity of the EGFR/TK inhibitor Tarceva™ (erlotinib, OSI-774) in tumor models

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Tarceva™ (OSI-774) is a potent, orally bioavailable, small molecule inhibitor of EGFR (HER1, erbB1) tyrosine kinase. Tarceva™ inhibits phosphorylation of the EGFR tyrosine kinase domain, thereby blocking key signal transduction molecules downstream from the receptor. Currently, Tarceva™ is in advanced clinical trials for several solid tumors, including NSCLC and pancreatic cancer. Treatment of tumor-bearing animals with Tarceva™ results in significant tumor growth inhibition (TGI) and regression in a variety of *in vivo* models of cancer. In the A431 human epidermoid xenograft model (high EGFR expression), Tarceva(TM) treatment causes tumor regression. Treatment of mice bearing H460a and A549 human NSCLC tumor xenografts (moderate EGFR expression) results in approximately 70% TGI. Tarceva™-induced tumor growth inhibition in animal models is dose-dependent, correlates with circulating levels of drug and with inhibition of phosphorylation of EGFR *in vivo*. In addition, using immunohistochemistry, we have evaluated the ability of Tarceva™ to inhibit cell proliferation and induce apoptosis in tumor cells, as well as studied its effect on tumor angiogenesis. Finally, we have studied the characteristic skin lesions observed in Tarceva™-treated