is 23 hours, and clearance 49 ml/h/m^2. BB10901 clearance is non-dose-proportional with greater clearance observed at lower dose levels perhaps secondary to NK cell binding. Two minor responses have been observed (1 neuroendocrine, 1 SCLC patient). BB10901 can be administered safely to patients with CD 56 expressing tumors with encouraging preliminary biologic activity observed. Patient accrual continues at 75 mg/m^2 weekly.

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Human Prostate Specific Membrane Antigen (PSMA) is expressed as a non-covalent dimer and provides an attractive target for cancer immunotherapy

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Prostate Specific Membrane Antigen (PSMA) is a type-2 membrane protein that is expressed abundantly on the surface of prostate cancer cells but not on normal human tissues. PSMA is also expressed on the neovasculature of a variety of other solid tumors. An antibody to the intracellular portion of PSMA is currently in use for *in vivo* imaging of prostate cancer, and the large extracellular portion of PSMA (707 of 750 amino acids) provides an attractive target for therapeutic vaccines. We have produced a recombinant soluble PSMA (rsPSMA) protein that comprises the entire ectodomain for use as a candidate vaccine. To compare the oligomeric nature of membrane-bound PSMA and the rsPSMA protein, we used gel filtration and Blue Native polyacrylamide gel electrophoresis, a novel high-resolution molecular sizing assay. The analyses indicate that PSMA is expressed as a non-covalent homodimer on the surface of LNCaP cells as well as on 3T3 cells stably transfected with full-length PSMA. In addition, rsPSMA was secreted as a non-covalent dimer from stably transfected Chinese hamster ovary cells, indicating that the extracellular residues of PSMA are sufficient for dimerization. Both, cell surface PSMA and rsPSMA, possess folate hydrolase and NAALADase activity and display similar patterns of reactivity with a panel of conformation-specific monoclonal antibodies. In contrast, the monomeric form of the protein exhibited only minimal enzymatic activity. In summary, PSMA is naturally expressed as a dimeric protein on the surface of prostate cancer cells. Only the homodimer form of PSMA is enzymatically active, may play an important role in tumor progression, and as such provides an attractive target for prostate cancer immunotherapy. To this end, we have developed rsPSMA, which faithfully mimics native PSMA in terms of tertiary and quaternary structure as well as enzymatic function. Thus, rsPSMA represents a promising candidate for evaluation as a therapeutic vaccine in combination with potent immunostimulatory adjuvants. *PSMA Development Company LLC is a joint venture between Progenics Pharmaceuticals Inc. and Cytogen Corp.

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A Phase II Study of Erbitux (IMC-C225), an Epidermal Growth Factor Receptor (EGFR) blocking ntibody, in combination with docetaxel in chemotherapy refractory/resistant patients with advanced Non-Small Cell Lung Cancer (NSCLC)

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EGFR has become an important target in cancer therapy as it is over-expressed in many solid tumors including NSCLC. IMC-C225 is a monoclonal antibody to EGFR that has demonstrated activity and synergy with chemotherapy in both preclinical and clinical settings. Docetaxel is the FDA approved 2nd line therapy for NSCLC. We investigated the combination of IMC-C225 and docetaxel as second-line therapy in chemotherapy refractory/resistant patients (pts) with advanced NSCLC. The objectives were to determine the tumor response rate, duration of response, survival, safety and toxicity, and pharmacokinetics (PK) of this combination therapy. Eligibility criteria included pts with advanced NSCLC who had progressive disease during or disease recurrence within 3 months after chemotherapy and tumor EGFR expression of at least 1+ by immunohistochemistry. IMC-C225 was administered as 400 mg/m^2 IV during the first week only followed by 250 mg/m^2 IV weekly. Docetaxel was administered at 75 mg/m^2 IV every 3 weeks.
Since May 8, 2001, we have enrolled 50 patients, 30 of which are evaluable for response and toxicity. Patient characteristics: 15 males and 15 females; median age 57 years (range 31-76); median ECOG PS 1 (0-2), and EGFR expression 3+ (25 pts), 2+ (3), 1+ (2). Thus far, 8 pts have achieved a partial response (5 confirmed and 3 unconfirmed) and 8 pts have stable disease. Median number of cycles is 3 (range, 1-10). Preliminary pharmacokinetic analysis shows no interaction of IMC-C225 with docetaxel. This regimen is very well tolerated with minimal toxicities including acneiform rash 7 pts (grade III/IV) and febrile neutropenia 3 pts (grade III/IV). IMC-C225 in combination with docetaxel appears to be well tolerated and the response rate suggests clinical activity in the second-line setting. Trial accrual has been completed. Final response data, duration of response and survival are still being collected.

Natural products

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A novel mechanism of potentiation of trail-induced apoptosis: resveratrol sensitizes resistant tumor cells for TRAIL by p21-mediated G1 arrest

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Since resistance of many tumors to current treatments protocols remains a major concern in oncology, novel strategies are necessary to target resistance. Here, we identify the chemopreventive agent resveratrol, a polyphenolic phytoalexin found in grapes and wine, as a potent sensitizer for TRAIL-induced apoptosis. Resveratrol strongly enhanced TRAIL-induced apoptosis through p21-mediated G1 cell cycle arrest indicating for the first time that sensitivity for TRAIL may be linked to cell cycle regulation. Also, resveratrol sensitized for apoptosis induced by CD95 triggering or by cytotoxic drug, e.g. doxorubicin, etoposide or cisplatin. Resveratrol-induced sensitization for TRAIL was mediated by rapid induction of p21 protein and G1 cell cycle arrest, since pretreatment with p21 antisense oligonucleotides abrogated the synergistic effect. Likewise, ectopic expression of p21 or pretreatment with the G1 cell cycle inhibitor mimosine strongly enhanced TRAIL-induced apoptosis. Induction of p21 by Resveratrol was mediated through p38 kinase-dependent p53 phosphorylation, since p53 phosphorylation and p21 induction was blocked by the p38 kinase specific inhibitor SB202190. Importantly, Resveratrol induced p21 expression also independent of wild-type p53 function, since p21 induction and sensitization for TRAIL treatment was found in p53 null Saos osteosarcoma cells or in p53-deficient HCT116 colon carcinoma cells. Resveratrol-induced G1 arrest resulted in rapid downregulation of Survivin protein expression, which was prevented by the proteasome inhibitor lactacystine, with no changes in Survivin mRNA expression. Likewise, Survivin antisense oligonucleotides enhanced TRAIL-induced apoptosis indicating that Resveratrol-induced potentiation of apoptosis was mediated by proteasomal degradation of Survivin at G1. Most importantly, synergy between resveratrol and TRAIL was found in a variety of different tumor types derived from neuroblastoma, medulloblastoma, glioblastoma, Ewing tumor, melanoma, pancreatic carcinoma, colon carcinoma, breast carcinoma or leukemia, and even in TRAIL-resistant cells and in patients' derived primary tumor cells. Therefore, by demonstrating that TRAIL-induced apoptosis is strongly enhanced by resveratrol through p21-mediated G1 arrest in a variety of tumors, our findings may have important clinical implication. Thus, the combination of TRAIL and resveratrol may be a novel strategy to overcome resistance of various tumors.

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Development of high-throughput *in vitro* and *in vivo* testing strategies for the discovery of novel anticancer agents of natural origin

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Natural products have proven to be a rich source of novel drugs. Their structural diversity offers excellent opportunities for finding low molecular weight compounds. The majority of anticancer agents which successfully completed clinical trials were of natural origin e.g. taxol or CPT-11. With the continuing need for novel lead structures against defined molecular targets, natural products will remain important to the future of anticancer drug discovery. We have opted to test a collection of over 5.000 chemically defined, pure natural products mainly from German Universities, and have developed high-throughput *in vitro* and *in vivo* testing strategies. The major obstacle in using isolated versus synthetic material is its limited availability - often only a few milligrams can be provided. We developped a cellular screen using 10 xenograft-derived human cell lines comprised of 7 slow or