NY-ESO-1 Ab was detected: in 1 pt after curative tumor resection, in 3 pts with PR of metastatic disease under therapy, and in 1 pt with a NY-ESO-1 – tumor relapse. Our results suggest that NY-ESO-1 Ab is dependent on the presence of NY-ESO-1 + tumors, reflecting the evolution of disease.

1433 ORAL

Clinical and immune responses in metastatic melanoma patients immunized with an anti-idiotype (anti-Id) monoclonal antibody (mAb) mimicking disialoganglioside gd21

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Purpose: We initiated a clinical trial for patients with metastatic melanoma treated with an anti-Id mAb (TriGem) that mimics GD2. The primary goal was to determine immune responses & toxicity; secondary goals were clinical responses & survival.

Patients & Methods: Forty-seven patients received either 1, 2, 4 or 8 mg doses of TriGem mixed with 100 μg of QS-21 adjuvant s.c. weekly × 4 then monthly until disease progression.

Results: Hyperimmune sera from 40 of 47 patients revealed an anti-anti-Id (Ab3) response. The 7 who did not generate an immune response progressed on study prior to the fifth injection. Patient Ab3 was truly Ab1 since it specifically bound to purified GD2. The Ab3 was predominantly IgG, with all IgG subclasses represented. One patient had a complete response, 17 patients are stable on study & 27 progressed and 20 have died. The Kaplan-Meier derived overall median survival has not been reached but at 16 months was 52%. Toxicity consisted of local reaction at the site of the injection & mild fever & chills.

Conclusion: TriGem has minimal toxicity, generates strong & specific IgG immune responses against GD2, & appears to have a major favorable impact on disease progression & survival.

1434 ORAL

Gene therapy for colon cancer using a novel deoxytidine kinase suicide gene together with cytosine arabinoside

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Purpose: Cytosine arabinoside (ara-C) is an effective drug for treatment of acute myeloid leukemia. However, it has only a limited validity against most GI tract tumors such as colon cancers. The reason includes relatively less amounts of deoxycytidine kinase (dCK) activity in non-myeloid cells. Here we hypothesized that solid tumors could be sensitized to ara-C if we successfully increased the cellular dCK activity. To verify the assumption, we transduced the dCK cDNA to mouse colon cancer cells and examined the efficacy of ara-C.

Methods: The MC38 mouse colon carcinoma cells were retrovirally transfected with dck cDNA. After selected with geneticin, expressors (MC38-dck) were isolated and comparedto the wild-type (MC38-wt) or control cells (MC38-neo). In order to examine the sensitivity, we performed cytotoxic assays. Next, we constructed an adenoviral vector containing dCK cDNA under the CMV promoter. Using this vector, we evaluated the in vivo efficacy of the dCK.

Results: Compared to other cells, MC38-dck cells were significantly sensitive to ara-C (IC50 = 488 pM). While MC38 cells transduced by control Ad.CMV-b-gal did not demonstrate differences in a sensitivity to ara-C, cells infected by Ad.CMV-dck exhibited an MOI-dependent increase of the sensitivity (MOI, 0 = 23.4 nM, MOI, 100 = 5.86 nM, MOI, 500 = 1.95 nM, respectively). When implanted subdermally, tumors of dCK-transduced MC38 cells were significantly smaller than of non-transduced cells after treatment of are-C ($p < 0.05$, two different measurments).

Conclusion: This system has numerous advantages for non-myeloid cancer gene therapy. First, since the dCK cDNA is human origin, it potentially limits the immunological responses. Next, the working concentration of the prodrug demonstrated in this study is easily achievable in the patients. Lastly, since ara-C is a classic agent, its pharmacokinetics is fully understood. Taken together, the dck/ara-C suicide system may be a potent approach for gene therapy of colon cancers.

1435 ORAL

Phase I-Study for patients with inoperable pancreatic carcinoma with encapsulated cells producing cytochrome P450 CYP2B1 that activates ifosfamide

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Background: Conventional chemotherapy of pancreatic carcinoma is only marginal effective. Substances such as ifosfamide, registered for the treatment of pancreatic cancer, have not been followed up due to a high toxicity at therapeutic doses.

Hypothesis: The local concersion of ifosfamide into its active components, phosphomustard and acrolein, should be feasable for treatment employing low systemic concentration of the drug.

Rationale: Transfection of CYP2B1 in cells with subsequent microencapsulation.

Experimntal Work: The enzyme activity (resorufin-essay) remains stable for weeks in vitro and in vivo within the microencapsulated CYP 2B1-expressing cells. We could demonstrate a significant antitumorous effect of the intratumorally injected capsules on xenotransplanted human pancreatic carcinomas on the nude mouse (Gene Therapy 1998, 5: 1070–1078). Angiographic experiments in pig assured the feasibility of an intraarterial placement of the capsules into the pancreas (Ann NY Acad Sci 1999, in press). A clinical protocol was established and approved (J Mol Med 1999, 77: in press).

Patients, Material and Methods: L293-cells were transfected with CYP2B1-gene, microencapsulated (diameter 0.5 cm) under GCP-conditions and packed sterile. Patients with confirmed inoperable adenocarcinoma of the pancreas underwent angiography and capsules were injected into a vessel leading to the tumor. The patients were monitored for 48 hrs to exclude allergic reactions or pancreatitis. A day later, ifosfamide was administered at 1000 mg/m^2 BS for three consecutive days to be repeated day 21–23. The patients were followed-up for 6 months.

Results: The study was opened 7/98. A total of 12 patients were enrolled; 5 of them finished the entire study period. In 10/12 patients the capsules could be administered as planned. In one patient, this was technically impossible. Another patient experienced an acute abdomen and had to be operated for an ileus. The 10 patients treated tolerated the procedure without any complications. No allergic reactions or pancreatitis was encountered. Chemotherapy was uneventful.

Discussion: The intraarterial application of microcapsules for targeted chemotherapyx was well tolerated. The antitumoral effects cannot be judged at present time.

1436 ORAL

Oral administration of chimeric MBO antisense-Protein Kinase A inhibits growth, angiogenesis and growth factors production and cooperates with cytotoxic drugs in human cancer xenografts

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Introduction: Protein kinase A type I (PKAI) plays a key role in neoplastic transformation and conveys mitogenic signals from different growth factors and oncogenes. Different pharmacologic tools developed to inhibit PKAI expression and function are able to inhibit cancer cell growth in vitro and in vivo. We have recently shown that a novel class of mixed-backbone oligonucleotides (MBOs) targeting the PKAI subunit RI, exhibit improved pharmacokinetic properties and antitumor activity in vitro and in vivo in several human cancer types.

Methods: We have administered orally HYB 165, a chimeric DNA/RNA MBO targeting the PKAI, alone and in combination with different cytotoxic drugs. We have evaluated the tissue distribution, the pharmacokinetic and the effect on tumor growth, angiogenesis and expression of several factors involved in the control of cell proliferation.

Results: We have demonstrated that the chimeric MBO HYB 165 has a good bioavailability and accumulates as intact oligo in the tumor after oral administration. As compared to a scramble MBO, oral HYB165 demonstrated a dose-dependent inhibition of the growth in human cancer xenografts in nude mice. Histochemical analysis showed that the antitu-