glial, neuronal and endothelial markers demonstrating pluripotency of differentiation potential. These findings point towards an essential role of CD133/Musashi-1+ cells in glioma biology making these cells a potential target for future therapies. On the other hand, stem cells are currently evaluated as potential carriers of anti-glioma therapies. Therefore, the second aim of our studies was to assess intracerebral distribution patterns of mesenchymal stroma cells (MSC) after local versus systemic application. Human MSC (hMSC) were isolated from bone marrow biopsies carried out for haematological indications. U373-GFP gliomas were generated by orthotopic implantation. After local application of hMSC, migration of hMSC towards the tumor was observed. In a second setting, intravenously administered MSC transfected with a RFP/Tie-2 promotor gene showed extensive tropism to the glioma. RFP expression indicated integration of MSC into the intratumoral vasculature. Therefore, MSC might be valuable candidates as carriers for an anti-tumor, especially an anti-vascular gene therapy. Altogether, stem cells might play roles in the "cause" as well as in the "cure" of glioma.

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S49. TARGETED DELIVERY OF CHEMOTHERAPY USING MICROENCAPSULATED CELLS FOR GDEPT

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Some of the most potent cytotoxic drugs, e.g. ifosfamide, are hampered in their effectiveness in certain cancers due to severe side effects in elder patients. A way to circumvent this problem is to employ gene directed enzyme prodrug therapy by delivering a second site of drug activation at the tumor site. This concept was developed using ifosfamide as the prodrug and the metabolising cytochrome P450 subenzyme CYP2B1 for conversion. The gene was transfected in 293 cells. To protect the genetically modified cells from the host immune system and, conversely, to protect the host from the allogenic cells, those were microencapsulated in sodium cellulose (diameter $\approx$ 0.8 mm). In an experimental setting, the microcapsules containing CYP2B1 expressing cells were directly injected in pre-established human pancreatic adenocarcinomas on nude mice. After treatment with low-dose ifosfamide, 20% CR was achieved. Identical results were obtained in a syngenic rat pancreatic carcinoma model. Further, this experimental approach has very successfully been applied to experimental peritoneal carcinomatosis as well as naturally occurring breast carcinomas in dogs. For clinical use, a feasibility study in pigs demonstrated the safety of agiographic intra-arterial placement into a pancreatic artery. After completion of IRB and registration with authorities, a clinical phase I/II study in patients with inoperable pancreatic adenocarcinoma was performed. The concept proved to be safe. 2/14 patients demonstrated a partial remission, the reminder was stable. Mean OS was 44 weeks, one year survival 32%.

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S50. DEVELOPING STRATEGIES FOR TUMOR VACCINATION

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Vaccination against cancer has had a variable history, with claims of success often fading into disappointment. The reasons for this include poor vaccine design, inadequate understanding of the nature of the immune response, and a lack of objective measures to evaluate performance. The characterization of tumor-associated antigens (TAAs) recognized by human T lymphocytes in a MHC-restricted fashion has opened new possibilities for specific vaccine approaches to the treatment of human cancers. Recent findings include vaccine formulation, relevant knowledge concerning mechanisms of induction of effective immunity from preclinical models, and translation into clinical trials. We now have novel vaccine strategies to activate specific attack on tumor cells and we understand more about activation and regulation of immunity against cancer (co-stimulation versus co-inhibition, regulatory T cells). We also have modern assays using surrogate markers (MHC multimer analysis, IFN-γ Elispot assay) to correlate with clinical effects. Although early clinical vaccine trials based on synthetic peptides, proteins, 'naked' DNA, tumor-RNA, dendritic cells, and recombinant vaccinia viruses indicate that vaccines can induce immune responses and tumor regression in some cancer patients, careful study design and use of standardized clinical and immunological criteria are needed. Basic principles of tumor vaccination and clinical trials will be discussed.

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S51. MOLECULAR STAGING OF THYROID CANCERS AND ASSOCIATED FAMILIAL SYNDROMES – CONSEQUENCES FOR SCREENING AND THERAPY

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Disseminated tumor cells in tissue, blood or bone marrow samples of patients with thyroid carcinoma are detectable by PCR assays by using different molecular tumor markers. The aim of our study was to correlate the results of molecular staging with the patients' follow-up.

Patients and Methods: Eighty-seven tumor, 43 blood and 14 bone marrow samples of patients with thyroid carcinomas were obtained during surgery and subjected to Cytokeratin 20 (CK20) and PreproGastrin-releasing peptide (PreproGRP) PCR systems.

Results: An expression of CK20 transcripts was detected in all of the medullary thyroid carcinomas (MTC), 63% of follicular thyroid carcinomas (FTC), 43% of papillary (PTC) and 17% of anaplastic (ATC) carcinomas . In FTC and PTC an expression of CK20 was seen in 54% in primary tumors and in 42% in soft tissue or lymph node recurrence. 75% of the patients with CK20-positive FTC were disease-free at follow-up compared to none of the patients with CK20-negative FTC. PreproGRP was found in 100% of MTC tissue samples. Overall, disseminated tumor cells of CK20-positive carcinomas were detected in 33% of the blood samples. In MTC,

preproGRP transcripts were found in 28% of the blood samples. The detection of a hematogenic tumor cell spread with preproGRP in MTC correlated significantly with advanced tumor categories. CK20 transcripts were detected in 75% of the blood samples of patients with thyroid carcinoma and distant metastases. Moreover disseminated tumor cells were detected in 21% of the bone marrow samples with CK20-PCR and 13% with preproGRP (only for MTC).

Conclusion: Both assays are sensitive enough to detect disseminated thyroid carcinoma cells in blood and bone marrow samples. However, the prognostic relevance of these disseminated tumor cells is not completely understood and has to be addressed in further investigations.

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S52. Pdcd4 TARGETS eIF4A TO INHIBIT TRANSLATION, TRANSCRIPTION, TUMORIGENESIS, AND INVASION

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Despite its name, Programmed Cell Death 4 (Pdcd4) may or may not induce apoptosis. Pdcd4 was discovered as a highly expressed gene in mouse JB6 cells resistant to transformation. Pdcd4 inhibits transformation and tumorigenesis, in part by specifically inhibiting AP-1 dependent transcription. The binding partners of Pdcd4 are not Jun or Fos proteins but are translation initiation factors eIF4A and eIF4G. Pdcd4 inhibits translation initiation by directly binding to translation initiation factor eIF4A and inhibiting its helicase activity. The helicase activity of eIF4A is important for unwinding 5′UTR structured mRNAs prior to scanning to the translational start site. Pdcd4 also interferes with scaffold eIF4G function. Pdcd4 must interact with eIF4A and inhibit translation in order to inhibit AP-1 transactivation, as Pdcd4 mutants inactivated for eIF4A binding fail to inhibit AP-1. Recent findings with K14-driven Pdcd4 expression in mice have established that Pdcd4 inhibits translation of a 5′UTR-structured mRNA as well as expression of "translationally repressed" proteins. Pdcd4 inhibits AP-1 dependent transcription and acts to attenuate papillomagenesis and papilloma to carcinoma conversion. Moreover Pdcd4 expression (a) is downregulated with progression in several human cancer sites, (b) confers sensitivity to certain therapeutic drugs, and (c) suppresses invasion and motility in human cancer cell lines. Pdcd4 suppresses cancer cell invasion by targeting the expression of MAP4K1, an upstream regulator of Jun N-terminal Kinase signaling, with consequent inhibition of AP-1 dependent transcription. Thus, activating or mimicking the expression of Pdcd4 might be an attractive preventive or therapeutic strategy. Enhancing the interaction of Pdcd4 with eIF4A or targeting downstream translational targets may produce the "desired" but not the "undesired" outcomes achieved with mTOR inhibitors. mTOR inhibitors repress translation by enhancing the interaction of 4E-BP with cap binding protein eIF4E but are also immunosuppressive. Pdcd4 appears not to show immunosuppressive activity. Although we and others have identified translationally repressed candidates, the functionally significant translational targets of Pdcd4 are still unknown. Knowing these Pdcd4 targets is important for designing prevention strategies. In summary, Pdcd4 is the first suppressor of tumorigenesis and invasion known to directly inhibit translation initiation. Translation initiation thus appears to be a promising molecular target for cancer prevention and intervention.

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S53. THE ISEL AND BR21 TRIALS – OUTCOMES SIMILAR OR DIFFERENT?

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The survival effects of EGFR-TKI therapy have been evaluated in two Phase III placebo-controlled studies in refractory NSCLC: ISEL (IRESSA Survival Evaluation in Lung cancer no. = 1692) and BR21 (erlotinib no. = 731).[1,2] Gefitinib (Iressa) showed some improvement in survival compared with placebo, but the difference did not reach statistical significance on the prespecified stratified log rank test required for registration in either the overall population (HR 0.89; $p = 0.087$; median 5.6 vs. 5.1 months) or in patients with adenocarcinoma (HR 0.84; $p = 0.089$; median 6.3 vs. 5.4 months). However, preplanned subgroup analyses showed that gefitinib significantly prolonged survival in patients of Asian ethnicity and in patients who had never smoked. The erlotinib BR21 study had a similar design to ISEL, but demonstrated a statistically significant overall survival benefit for erlotinib HR = 0.7 $p < 0.001$ median 6.7 vs. 4.7 months.[2] However the 95% confidence intervals for the HRs overlap ISEL 0.77–1.02 and 0.58–0.85 for BR21