different fungal species – that inhibit centrosomal clustering and thus force tumor cells with supernumerary centrosomes to undergo multipolar mitoses and consequently apoptosis.
Results: This approach led to the identification of several substances which are currently characterized in more detail. One of these substances is the well-known antifungal drug griseofulvin, which, in addition to its inhibition of centrosomal clustering described here, has recently been shown to suppress microtubule dynamic instability.
Conclusion: Taken together, this screening may help identify new potential anti-cancer drugs.

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P47. RADIOPROTECTION OF NORMAL TISSUE CELLS BY TRANSFER OF THE HUMAN SUPEROXIDE-DISMUTASE GENE

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Background: Protection of normal tissue against radiation-induced damage would increase the therapeutic ratio of radiotherapy. A promising strategy for this approach is gene therapy-mediated overexpression of copper–zinc (CuZnSOD) and manganese superoxide-dismutase (MnSOD). Recombinant adeno-associated virus 2 (rAAV2) are attractive vectors owing to their ability to infect non-dividing cells and a very low risk of insertional mutagenesis. The purpose was to test the radiomodulating effects of SOD on human primary lung fibroblasts (HPLF).
Methods: Low passage HPLF (MRC5) cells were transduced with the rAAV2-SOD vectors, harvested on day 3, irradiated (1–8 Gy) and analysed using FACS, Western blot, SOD-activity and colony formation assays.
Results: High transduction rates were obtained with >80% of the HPLF cells expressing the respective SOD. Compared to transduction controls, CuZnSOD did not exhibit any radioprotective effects, whereas for MnSOD-transduced HPLF an increase of approximately 30% in the survival of colony-forming cells was observed (1–4 Gy).
Conclusion: An increase in clonogenic survival (1.3-fold) of HPLF cells after transfer of MnSOD and subsequent irradiation was shown. Earlier, we have shown lack of protection in tumour cells (HeLa), thus supporting that MnSOD may increase the therapeutic ratio. rAAV2 vectors are promising tools for the delivery of radioprotective genes in normal tissue such as the lung for pulmonary or intestine cells for prostate irradiation.

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P48. GONADOTROPHIN RELEASING HORMONE BASED VACCINE (GnRHm1-TT), AN EFFECTIVE CANDIDATE FOR HORMONEDEPENDENT CANCER IMMUNOTHERAPY

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Background: The normal development and functioning of the prostate gland, as well as its benign and neoplastic growth is dependent of androgen. Previous studies with Gonadotrophin Realeasing Hormone (GnRH/LHRH) vaccines, have shown the usefulness of immunization against this hormone in prostate and breast cancer.
Methods: In this work we have designed a vaccine candidate called GnRHm1-TT based on a completely synthetic immunogen. The peptide was formulated as a white semiviscous water in oil preparation and injected to animals.
Results: In healthy animals, this vaccine candidate showed to be very immunogenic, resulting in high anti-GnRH antibodies titers, testosterone reduction and significant decrease of the prostate and testicle weight. In tumor implanted rats the vaccine candidate had demonstrated to produce significant tumor growth inhibition of Dunning R3327-H androgen responsive prostate tumor in rats $P = 0.025$ and survival increase, $P = 0.001$.
Conclusion: GnRHm1-TT have demonstrated to be highly immunogenic and safe, causing prostate and testicle atrophy and significantly tumor growth inhibition. These results make our vaccine candidate useful as an effective androgen deprivation therapy, and possible application to prostate cancer and other hormone-dependent malignancies therapy.

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P49. ZOLEDRONIC ACID HAS DIRECT ANTI-PROLIFERATIVE AND ANTI-METASTATIC EFFECT ON PANCREATIC CARCINOMA CELLS AND ACTS AS AN ANTIGEN FOR δ2 γ/δ T CELLS

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Background: Beside their use as anti resorptive drug, bisphosphonates are well known to stimulate γδ T cells and to have direct effects on tumor growth.
Methods: We determined the direct cytotoxic effect of pamidronate and zoledronic acid, the induction of apoptosis and their anti-metastatic potential. Next, we analyzed how bisphosphonates act on γδ T cells propagated with our recently published protocol. The susceptibility of pancreatic carcinoma cells pretreated with bisphosphonates against γδ T cells was tested in cytotoxicity assays and the subgroup involved in killing was investigated.

Results: Zoledronic acid but not pamidronate has a cytotoxic potential even at pharmacological dosage. Zoledronic acid does not only induce apoptosis by inhibiting the Ras-pathway but has also an anti-metastatic effect. Freshly prepared γδ T cells consisting mainly of Vδ2 cells showed increased cytotoxicity against bisphosphonate-treated pancreatic carcinoma cells. γδ T cells could be expanded fourfold by use of anti-CD3 and IL-2. However, activated. γδ T cells do not respond to bisphosphonates and kill mainly in a Vδ1 dependent manner.
Results: Our results demonstrate that zoledronic acid has a direct apoptotic effect on pancreatic carcinoma cells and has anti-metastatic properties. Tumor cells treated with zoledronic acid are more susceptible against Vγ9 Vδ2 T cells, the most abundant population of γδ T cells in the peripheral blood. Treatment with zoledronic acid for patients with pancreatic carcinoma might be an option.

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P50. THE TETRASPANIN D6.1A INDUCES TUMOR ANGIOGENESIS

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Background: Tetraspanins are involved in cell activation, proliferation, adhesion, motility and cell fusion. Some members including D6.1A are known to promote metastasis formation. Overexpression of the tetraspanin D6.1A on a rat pancreatic adenocarcinoma line BSp73AS (BSp73AS-D6.1A) is associated with the formation of haemorrhagic ascites and can induce disseminated intravascular coagulation.
Methods: Angiogenesis was analysed by intravital microscopy of the rat mesentery 6 days after intraperitoneal tumor cell application and after co-culture of the mesentery with tumor cells, supernatant of the tumor cells and tumor cell derived exosomes.
Results: D6.1A expressing tumor cells induced strong angiogenesis with vessels covering roughly 25% of the tumor area as compared to 5% in BSp73AS tumors. Also mesenteric cells displayed strikingly increased branching in co-cultures with BSp73AS-D6.1A cells, supernatant thereof or tumor cell derived exosomes. A D6.1A-specific antibody completely inhibited BSp73AS-D6.1A-, but also BSp73AS-induced angiogenesis in vivo and in vitro. This finding suggested the existence of an additional antibody target that has been identified as proliferating endothelial cells, which strongly upregulate D6.1A expression.
Conclusion: Tumor derived D6.1A is a strong angiogenesis inducer, that indicates for an angiogenic loop due to the striking upregulation of D6.1A on endothelial cells. Because of the latter, the antibody-mediated suppression of the angiogenesis likely offers a very effective and selective drug.

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P51. DEFINING THE APOPTOTIC PATHWAYS UNDERLYING HISTONE DEACETYLASE INHIBITOR-MEDIATED TUMOR THERAPY

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Background: Histone deacetylase inhibitors (HDACi) are novel anti-tumor compounds currently being tested in clinical trials. Our laboratory has previously shown that in cultured cells HDACi-induced cell death was mediated by mitochrondrial damage, cytochrome C release and Bid cleavage. However, it is presently unclear which apoptotic pathways are utilized by HDACi in vivo, i.e. in a therapeutic setting. Moreover, it is poorly understood how molecular events during anti-cancer drug-mediated apoptosis relate to therapeutic outcome.
Methods: We have employed the murine Eμ-myc B-cell lymphoma model to directly compare HDACi-induced cell death in vitro with therapeutic efficacy in vivo. Our system comprises lymphomas with defined genetic alterations in the apoptotic machinery and the tumors can either be grown and treated in culture or transplated into immunocompetent animals for therapy studies. Using this system, we have identified key apoptotic molecules that not only control sensitivity of cultured lymphoma cells to HDACi, but also determine therapeutic outcome.
Results: Overexpression of Bcl2, previously linked to treatment failure in human cancers, conferred complete chemoresistance in vitro and in vivo. Strikingly, the HDACi SAHA eradicated Eμ-myc lymphomas in a p53-independent manner, resulting in prolonged survival after SAHA treatment of p53−/− lymphomas. Constraining the cellular apoptotic program by genetic targeting of Apaf-1, Caspase-9 and Bid impinged on in vitro sensitivity and we are currently investigating whether this is associated with tumor relapse and chemoresistance while animals are under therapy.

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P52. ASSOCIATION OF DNA-REPAIR POLYMORPHISMS WITH SURVIVAL IN LUNG CANCER PATIENTS

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Introduction: The X-ray cross-complementing gene *XRCC1* and the excision repair cross-complementing group 2 gene *ERCC2* (*XPD*) are involved in the repair of DNA modifications resulting from DNA-damaging agents used in cancer therapy. Functional