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

Sabine Gesierich[a], Igor Berezovskiy[a], Eduard Ryschich[b], Margot Zöller[a]. [a]*Department of Tumor Progression and Immune Defense, DKFZ, Heidelberg, Germany;* [b]*Department of Surgery, University of Heidelberg, Germany.*

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

Ralph K. Lindemann[a], Andrea Newbold[a], Kate Whitecross[a], Anthony E. Dear[b], Clare L. Scott[c], Andrew Wei[c], Victoria Richon[d], Scott W. Lowe[e], Ricky W. Johnstone[a]. [a]*Peter MacCallum Cancer Centre, Cancer Immunology Program, Gene Regulation Laboratory, East Melbourne, Vic. 3002, Australia;* [b]*Monash University, Department of Medicine, Box Hill Hospital, Vic., Australia;* [c]*The Walter and Eliza Hall Institute of Medical Research, 1G Royal Parade, Parkville, Vic. 3050, Australia;* [d]*Merck and Co. Inc., Boston, MA, USA;* [e]*Cold Spring Harbor Laboratory, Bungtown Road, Cold Spring Harbor, NY 11724, USA.*

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

H. Dally[a], S. Tuengerthal[b], P. Drings[b], J.R. Fischer[c], L. Edler[a], B. Jäger[a], O. Popanda[a], B. Spiegelhalder[a], H. Bartsch[a], A. Risch[a]. [a]*German Cancer Research Center, Heidelberg, Germany;* [b]*Thoraxklinik, Heidelberg, Germany;* [c]*Klinik Löwenstein, Germany.*

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