The concept of "G2 checkpoint abrogation" in combination with various chemotherapeutic drugs is currently successfully explored in clinical trials. The anti-cancer drug UCN-01 allows the entry into mitosis in the presence of DNA damage selectively in p53 defective tumor cells.

We show here that this leads to a mitotic arrest and to the activation of a branch of the mitotic spindle checkpoint that monitors the lack of tension across kinetochores involving the function of Mad2, Bub1, BubR1, Mps1, Aurora B and survivin. Subsequently mitotic cell death, also known as "mitotic catastrophe", is induced, which potentiates the efficacy of standard chemotherapy. Interestingly, mitotic cell death is associated with the activation of the mitochondria associated apoptosis pathway, thus, we refer to it as mitotic apoptosis. Importantly, while the mitotic arrest in response to UCN-01 is dependent on the spindle checkpoint, only the checkpoint component Mad2 is required for the execution of mitotic apoptosis suggesting that Mad2 might have an additional function as a pro-apoptotic protein. Significantly, the mitotic apoptosis is counteracted by a survivin dependent survival pathway. Thus, the mitotic apoptosis is a result of a balance between pro- and anti-apoptotic pathways. Most importantly, pharmacologiocal interference with Aurora B, CDK1 or PI3-kinase modulating the levels of survivin leads to a significant increase of apoptosis in response to UCN-01. Thus, our results suggest a highly improved strategy for anti-cancer treatment using UCN-01 and abrogators of a mitotic survivin dependent survivial pathway without neglecting the selectivity of UCN-01 for p53 defective cancer cells.

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S36. VIRAL ONCOGENES CAUSING HUMAN CANCERS

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Research of the past 25 years resulted in the identification of a number of infectious agents engaged in the etiology of in part very common human cancers. Among the latter are cervical cancer and hepatocellular carcinomas. Members of several different virus families possess oncogenic potential: these are papillomaviruses (e.g. HPV 16 and 18), herpes group viruses (Epstein-Barr virus and human herpesvirus type 8), Hepatitis B and Hepatitis C virus, Human T-lymphotropic retrovirus type 1 (HTLV-1). Most of these agents contain oncogenes and act as "direct carcinogens". The functions of these oncogenes have been partially characterized and will be discussed. Humans and their cells infected by these viruses are commonly able to cope with these infections by intra- and intercellular surveillance mechanisms or by immunological interference. Cancer development requires a modification of genes within the signalling pathways regulating the intra- and intercellular defense. Part of the modifications of cellular genes is also mediated by viral oncogenes.

Besides direct carcinogenic functions via oncogenes, other agents contribute to human cancer by rather indirect modes. This seems to be the case in hepatitis B and C infections where the induction of oxygen radicals apparently plays a significant role in cancer induction. Human immunodeficiency viruses (HIV) promote cancer induction by other viruses due to the induction of immunosuppression. Possible other mechanisms of indirect carcinogenesis by infectious agents will also be discussed.

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S37. ONCOPROTECTIVE PARVOVIRUSES IN CANCER THERAPY

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As a result of their oncotropism, oncolytic effect and low inflammatory activity, some autonomous parvoviruses open up new prospects to the fight against cancer and were tested for their safety in pilot phase I clinical trials. Preclinical studies in animal models showed that the parvoviruses H-1PV and MVM are endowed with a genuine oncosuppressive capacity, for which various tumours can be targets. However, the antineoplastic potential of these agents is insufficient, in many instances, for tumours to irreversibly regress. Efforts are thus made to improve the oncosuppressive activity of parvoviruses, using different strategies. On the one hand, discrete modifications are introduced into the parvoviral genome so as to keep its infectiousness while stimulating its antineoplastic properties. Parvovirus mutants were engineered so that their capacity for tumour cell lysis or immune cell activation is enhanced. On the other hand, parvoviruses are used as vectors to generate recombinants that are able to deliver therapeutic transgenes in target cells. MVM and H-1PV-based vectors transducing and expressing anti-angiogenic and/or immunomodulating factors were more particularly produced. Appropriate combinations of these recombinant vectors were found to efficiently suppress highly vascularised tumours, e.g. gliomas, in animal models. On the basis of these data, the promise of the application of parvoviruses to cancer viro- and gene therapy will be discussed.

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S38. PROPHYLACTIC VACCINES AGAINST CERVICAL CANCER

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Since several years it has been accepted that persistent infection with certain (so called-high risk: HR) types of Human papillomaviruses (HPV) represents a strong risk factor for cervical cancer. The most frequent HR HPV types 16 and 18 account for about 70% of this tumour, which is the second most frequent malignancy in women worldwide. Several studies in animal papillomavirus models revealed that protection against infection is conferred by neutralizing antibodies directed against conformational epitopes of the major structural protein L1. Such antibodies can most efficiently be induced by immunization with virus-like particles (VLP) that assemble spontaneously following expression of L1 in recombinant vectors. Large-scale production of HPV 16 and 18 VLPs proved to be successful facilitating, a few

years ago, first clinical trials on safety and immunogenicity. In the meantime more than 25,000 women have been included into several efficacy trials which demonstrated protection against persistent infection with HPV 16 and 18 and against the development of precursor lesions to cervical cancer. Although the ultimate proof of success, i.e. reduction of cancer incidence still requires the immunization of large populations and many years of follow-up, the existing data are so persuasive that the first marketing of the vaccine is expected to be announced in mid 2006. Yet several questions such as the duration of protection, the need development of for post-exposure vaccination strategies and availability of such vaccine in low-budget countries are open and will be discussed.

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S39. IDENTIFICATION OF POTENTIAL TARGET ANTIGENS FOR IMMUNOTHERAPY APPROACHES

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Immunotherapy approaches in cancer rely on the identification of suitable antigens that can be used as targets for therapeutic approaches. The ideal target antigen is highly and homogenously expressed in cancer, but not or low level expressed in normal tissues. Using different cloning techniques, several potential target antigens have been identified, some of these antigens are already being evaluated in clinical trials. We followed a cloning strategy called SEREX that identifies tumor antigens based on a spontaneous humoral immune response in patients. Using this technique we identified 2 new tumor associated antigens that belong to the group of differentiation antigens: NY-BR-1 as a new breast differentiation antigen and RAB38/NY-MEL-1 as a new melanocyte differentiation antigen.

NY-BR-1 is not expressed in normal tissues except in normal mammary gland and testis, but it is highly expressed in 70% of breast cancers. Antigen positive cancers maintain the expression in metastatic lesions. Spontaneous antibody responses occur in about 10% of breast cancer patients. We identified 2 HLA-A2 restricted NY-BR-1 derived epitopes that were recognized by CD8+ T cells from patients with NY-BR-1 expressing cancers. Both epitopes are naturally processed and presented.

RAB38/NY-MEL-1 is expressed in melanocytes and at low level in adrenal gland, all other normal tissues are RAB38/NY-MEL-1 mRNA negative. Spontaneous humoral immune responses are frequent in melanoma patients but not in normal individuals, in patients with vitiligo or with cancers other than melanoma. We recently identified a HLA-A2 restricted RAB38/NY-MEL-1 derived epitope that is naturally processed and presented and recognized by CD8 T cells.

Both new antigens, NY-BR-1 and RAB38/NY-MEL-1 are being evaluated as targets for T cell based immunotherapy strategies in Phase-I trials.

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S40. T CELL BASED IMMUNOTHERAPY – CHANGES AND CHALLENGES

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Advances in cellular and molecular immunology have led to the development of strategies for effective augmentation of anti-tumor immune-responses in cancer patients. This presentation focuses on the manipulation of T cell immunity either by active-specific immunization with tumor vaccines[1–4] or by adoptive immunotherapy with immune T cells.[5,6] Such therapies offer exquisite specificity of tumor recognition based on the ability of the T cell to distinguish single amino acid differences in any protein from any compartment of the tumor cell.

Recent analyses of bone marrow samples from patients with a variety of different cancers revealed the existence of cancer reactive memory T cells in a high proportion and at high frequencies.[5–9] A fine specificity analysis revealed *individuality* (i) of response patterns to multiple tumor associated antigens (TAAs), (ii) of the size and (iii) of the specificity of the memory repertoire in the bone marrow of cancer patients. These findings challenge immunotherapy approaches targeting single TAAs. Future strategies will be discussed for the exploitation of the TAA memory repertoire of cancer patients. In "proof of principle" studies it was demonstrated to have great therapeutic potential.[5,6]

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S41. TARGETING THE APOPTOTIC PATHWAY TO INDUCE RADIORESISTANCE IN NORMAL TISSUE AND STEM CELLS

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Novel strategies in clinical radiotherapy have the goal to increase the therapeutic index i.e. effective tumor cell kill while sparing the normal tissue. This can be achieved by either physical selectivity when the tumor is well circumscribed or by biological selectivity when normal tissue is present in the treatment volume. Biological selectivity can be achieved by targeting tissue properties which are only present either in tumor or normal tissue cells.

Radiation induced apoptosis is a rare event as compared to mitogenic death in epithelial tumor cells. In contrast, radiation