Research Program Applied Tumor Virology
Coordinator: Prof. Dr. Jean Rommelaere

Tumor Virology (F0100)
Prof. Dr. (PhD) Jean Rommelaere
☎ 06221 42-4960, FAX 06221 42-4962
e-mail: J.Rommelaere@DKFZ.de

Genome Alterations and Carcinogenesis (F0200)
Prof. Dr. rer. nat. Lutz Gissmann
☎ 06221 42-4603, FAX 06221 42-4932
e-mail: L.Gissmann@DKFZ.de

Tumor Virus-Immunology (F0300)
Prof. Doz. Dr. rer. nat. Frank Rösl (provis.)
☎ 06221 42-4900, FAX 06221 42-4902
e-mail: F.Roesl@DKFZ.de

Virus-Host-Interactions (F0600)
Prof. Dr. rer. nat. Claus H. Schröder (provis.)
☎ 06221 42-4850, FAX 06221 42-4852
e-mail: C.Schroeder@DKFZ.de

Tumor Virus Characterization (F0700)
Prof. Dr. (D. sc.) E.-M. de Villiers
☎ 06221 42-4614, FAX 06221 42-4822
e-mail: E.Devilliers@DKFZ.de

Retroviral Gene Expression (F0800)
Prof. Dr. rer. nat. Rolf Flügel
☎ 06221 42-4611, FAX 06221 42-4865
e-mail: R.M.Fluegel@DKFZ.de

The Research Program „Applied Tumor Virology“ (ATV) focuses on the role of viruses in human cancer diseases, the mechanisms of virus-induced neoplastic transformation and host defense reactions against viral oncogenesis. Special interest lies in the relations of human papillomaviruses with genital, oropharyngeal and skin cancers, and of hepatitis B and C viruses with hepatomas. In particular, the regulation of viral gene expression by cellular factors and the interaction of virally encoded oncoproteins with cellular growth regulators are studied. This fundamental research is accompanied with the development of novel tools for the diagnosis, prevention and treatment of tumor virus infections and diseases. Innovative treatments include gene therapy approaches on which emphasis is laid in the ATV Program through the production and validation of new virus-based vectors and effector genes. Vector-oriented research concerns more particularly the assessment and optimization of the capacity of helper-dependent and independent parvoviruses, polyomaviruses, spumaviruses and lentiviruses for foreign gene transduction and expression. Attempts are also made at elaborating effector genes, the products of which can potentially be used to control papillomavirus, HIV and prion infections, or to sensitize cancer cells to radio-/chemotherapeutic agents.

The Tumor Virology Division has continued its research in the field of „biological antitumor strategies“. These strategies comprise: (A) the therapeutic use of paroviruses, and (B) the specific blocking of cellular DNA repair mechanisms. (A) Helper-dependent and independent paroviruses are being investigated to determine their potential as antitumor effectors and as vectors for gene therapy. Basic research in this direction is essential to maximize the tumor cell-specific paroviral attack. In this respect the molecular mechanisms determining the intracellular oncotropism of autonomous paroviruses as well as the cytotoxic functions of the viral proteins are of major interest. The applied research includes optimization of vector packaging systems as well as the analysis of certain antitumor genes for the production of recombinant paroviruses with antineoplastic potential. (B) Infection of various human tumor cells with adeno-associated virus (AAV) was found to increase the sensitivity of the tumor cells to cytostatic drugs and radiotherapy in vitro and in vivo, and may revert resistance to chemotherapy. The molecular mechanisms involved in this phenomenon have been characterized further and examined for their therapeutic potential. In addition, the infectiology of the natural infection with AAV is studied to gain information on natural target tissues for these viruses and to assess potential pathological effects. Another method of sensitizing cells to the effects of DNA mutagens involves the expression of a dominant negative mutant of the poly(ADP-ribose) polymerase enzyme, which in its normal form recognizes DNA strand breaks and leads to the synthesis...
of protein-linked poly ADP-ribose. The mechanisms involved have been investigated and the results obtained provide a sound basis for further developing this approach towards antitumor gene therapy.

A major interest of the Division of Genome Alterations and Carcinogenesis concerns the molecular mechanisms by which human papillomaviruses (HPV's) transform and malignize cells, and aims at the development of strategies to diagnose, prevent and reverse this process. These strategies include therapeutic and preventive vaccines against HPV as well as ribozyme and antisense approaches for potential treatment and suppression of aberrant and pathogenic gene expression. Our further interest concerns the replication of HIV-1 with an emphasis on glycoprotein incorporation into HIV-1 particles and targeting of lentiviral vector particles.

The Division of Tumor Virus Immunology is presently changing its structure. PD Dr. Frank Rösl has been nominated as provisional head of this division. His group is predominantly engaged in the analysis of the intra- and intercellular regulation of persisting high-risk human papillomaviruses. Another research aspect is the study of the biological effects of cytokines and chemokines in certain tumor virus-host cell systems. Furthermore, a new section, headed by Dr. Martin Müller has also been established. His group is mainly performing structural and functional analyses of papillomavirus capsid proteins. Another independent research group, "Mechanisms of pathogenesis of tumor virus infections" is headed by Prof. Dr. Dr. h.c. mult. Harald zur Hausen. The activities encompass several small groups who find a platform for their own development into independent units. Priorities are functional aspects of viral oncoproteins, their interaction with host cell factors and the development of new diagnostic and preventive tools in the control of tumorvirus infections.

Subject of research in the Division Virus-Host-Interactions is the role of papillomaviruses (HPV) and of the Hepatitis B virus (HBV) in the genesis of cervical cancer and liver carcinoma, respectively. A focus is on oncoproteins and potentially oncogenic proteins expressed by chromosomally integrated and free viral DNA. For HPV, the emphasis is on the regulation of the transcription of E6 and E7 and on the analysis of E6 function, for HBV, on the identification of stages of the chronic infection critical for hepatocarcinogenesis. In addition, new strategies are developed to interfere with the growth of cervical carcinoma cells, to inhibit HBV replication, and to improve the diagnosis of HBV infection. Alterations of chromosomal DNA at the site of HPV DNA integration are being described aiming at the identification of cellular genes critical for maintaining the normal, untransformed phenotype.

The Division for Tumorvirus Characterization analyzes the role of viruses in human cancer development. The majority of studies aim at the characterization of novel tumorvirus types and at the analysis of viral/host cell protein interactions. The division has recently been able to identify an additional 37 novel human papillomavirus (HPV) genotypes, mainly from squamous cell carcinomas of the skin, the aerodigestive tract and the esophagus, but also from normal skin biopsies. During the past year 70 novel TT virus genotypes have been partially characterized - their potential role in the stimulation of cell growth remains to be investigated. Degenerate primers have been developed and used for searching for the polyoma- and herpes-groups of viruses in human tumors. In addition, the molecular mechanism by which cutaneous HPV types, intracellular regulatory components and cytokines interact in malignant cells will continue to be the focus of special interest. Examination of the interaction between viral oncoproteins and cellular factors led to the discovery of a ubiquitin-dependent proteolysis system and additional proteins that were able to bind to this complex.

The goals of the research being carried out within the Division of Retroviral Gene Expression are to better understand the mechanisms of gene expression employed by the human spumaretrovirus (HSRV) as well as the interaction of HSRV proteins with the host cell and changes resulting from these interactions. The viral transactivator induces the expression of distinct sets of human genes including those of the imprinted genes insulin-like growth factor and cyclin-dependent protein kinase inhibitor, p57Kip2. The aim is to explore the mechanisms of transactivation. In the long term, novel vectors from which larger coding regions can be expressed - compared to standard retroviral systems - will be used in gene transfer experiments.