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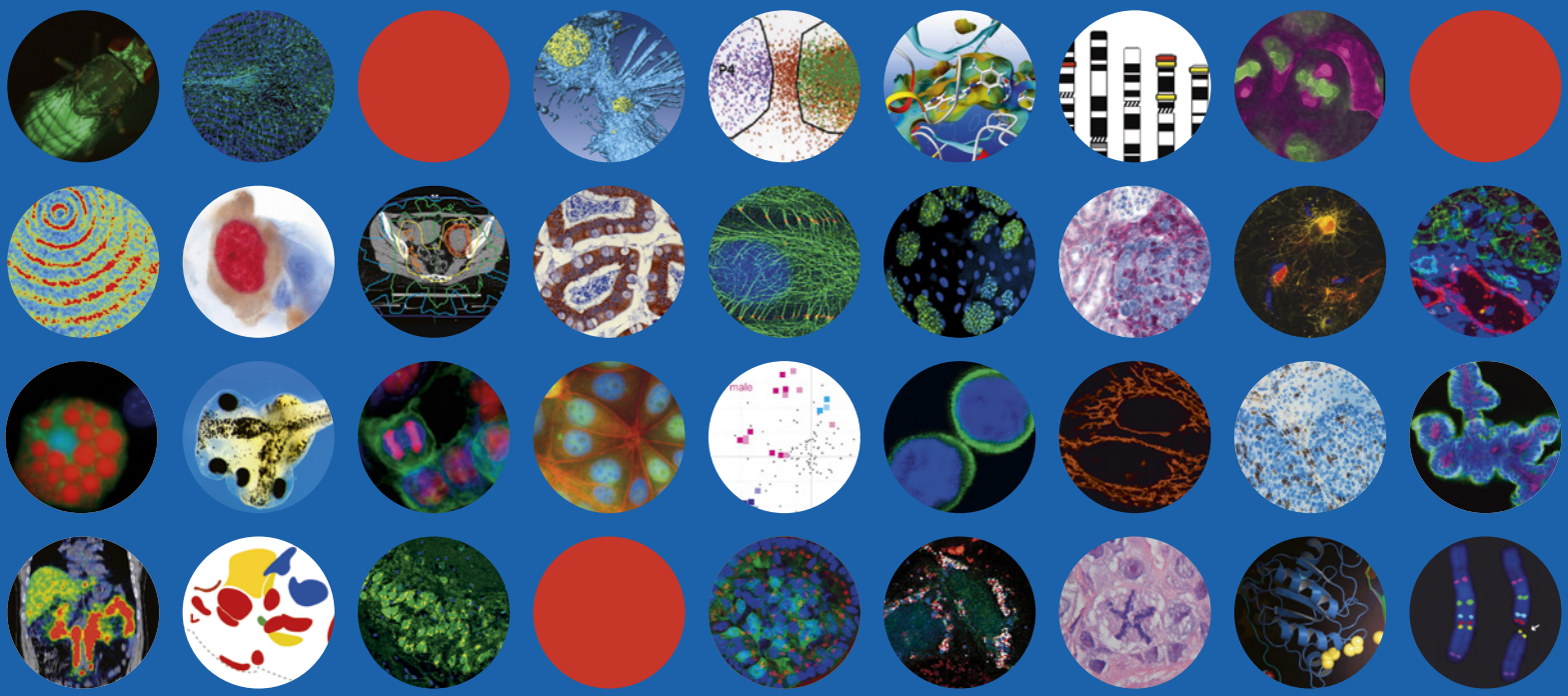
GERMAN
CANCER RESEARCH CENTER
IN THE HELMHOLTZ ASSOCIATION

Research for a Life without Cancer

Cancer Research at DKFZ 2016



Research Program

INFLAMMATION, INFECTION AND CANCER

RESEARCH PROGRAMS

The DKFZ covers the entire breadth of modern cancer research. Fields of research range from knowledge of the molecular basis of the development of cancer, distribution and risk factors within the population to diagnosis and treatment.

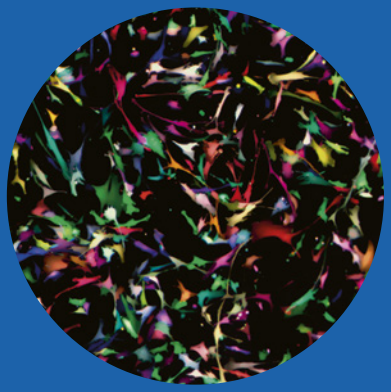
As an interdisciplinary environment, DKFZ employs scientists with qualifications in medicine, biology, biochemistry, physics, chemistry, mathematics, informatics or related issues. More than 100 division heads, group leaders and senior scientists, 200 postdocs and about 400 PhD students work together at the Center.

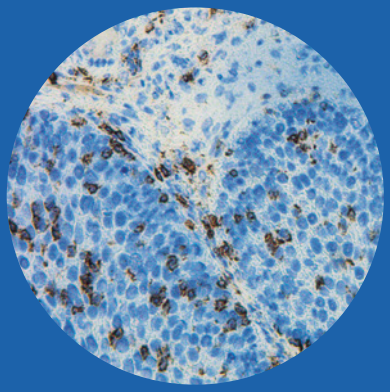
At the DKFZ, researchers benefit from intensive scientific exchange between research programs and individual groups, which serves as the basis for the internationally renowned research at the Center.

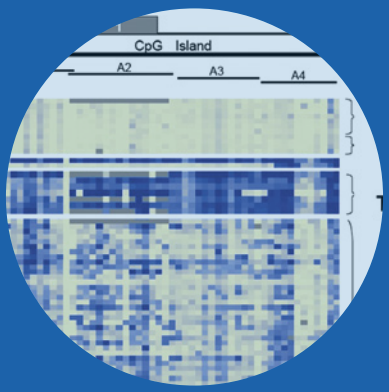
Research groups are organized into seven research programs:

- Cell Biology and Tumor Biology
- Functional and Structural Genomics
- Cancer Risk Factors and PreventionTumor Immunology
- Imaging and Radiooncology
- Infection, Inflammation and Cancer and
- Translational Cancer Research.

In the German Cancer Consortium (DKTK), one of six German Centers for Health Research, the DKFZ maintains translational centers at seven university partnering sites. Combining excellent university hospitals with high-profile research at a Helmholtz Center is an important contribution to improving the chances of cancer patients (see also pages 150ff).



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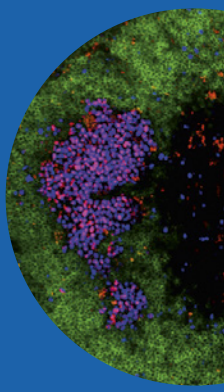
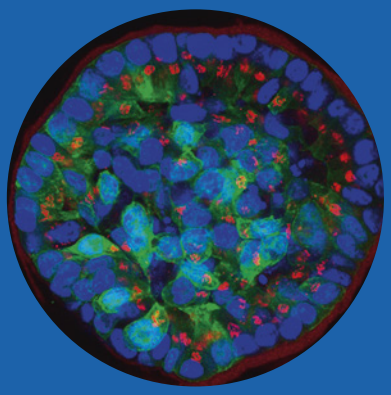
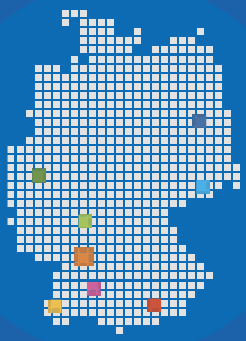
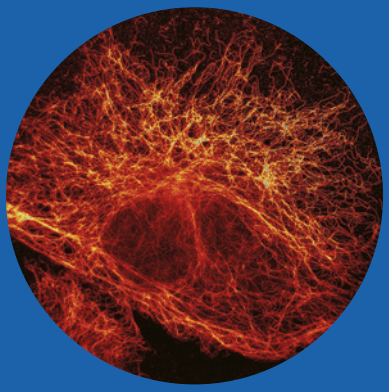
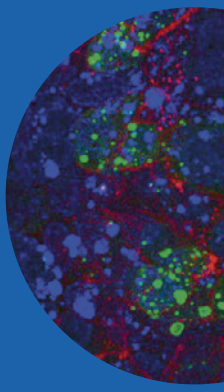








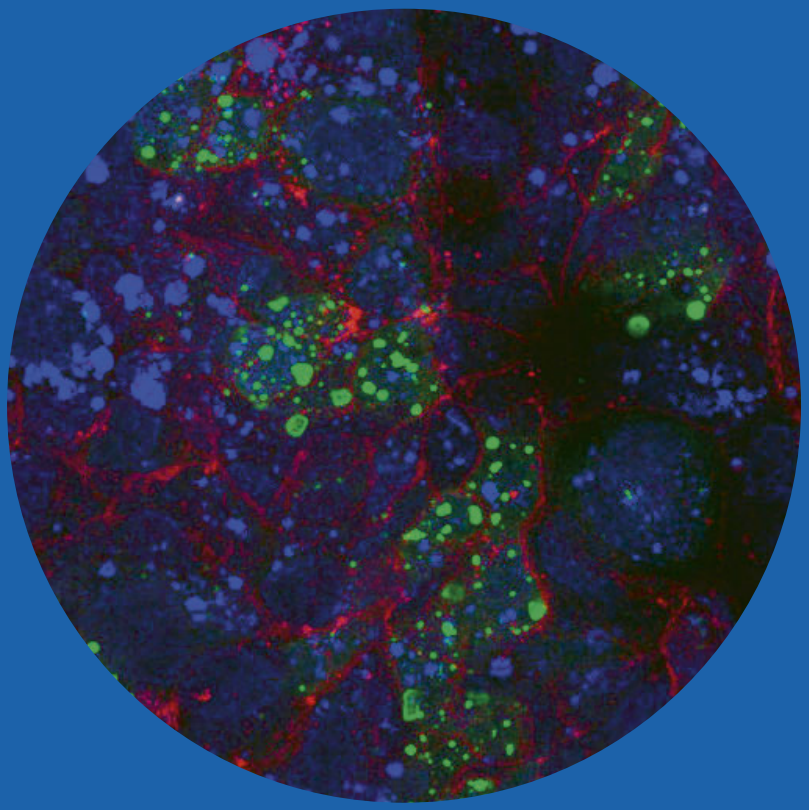


Coordinator
Prof. Dr. Ralf Bartenschlager

Infection, Inflammation and Cancer

Infections with pathogens play a crucial role in a number of cancers. This Research Program investigates viruses promoting tumor development, the mechanisms of infection-associated inflammation and carcinogenesis and how the human body defends – or fails to defend – against these events. The work of the Research Program aims to improve the diagnosis, prevention, and treatment of such viral infections as well as their associated tumors. By means of epidemiologic studies, we analyze the success of newly established relevant therapies or vaccines and aim to identify yet-unknown associations between viruses and tumor entities. Furthermore, scientists of the Research Program are developing viruses to be used for the selective killing of cancer cells or as vehicles for introducing therapeutic genes into cells. In a nutshell, the main research topics of the Research Program are:

- Papilloma viruses and their role in cancer
- Pathogenesis of cancers caused by infection with the Epstein-Barr virus
- Chronic infections with hepatitis viruses and their role in liver tumor formation
- Infectious DNA agents in cancer and chronic diseases
- Chronic inflammation and its link to tumor formation
- Molecular diagnostics of oncogenic infections
- Development of innovative therapies: oncolytic viruses and novel gene vectors
- Vaccines against human papilloma viruses and Epstein-Barr virus



AWARDS AND GRANTS

Professor Ralf Bartenschlager:
Robert Koch Prize 2015

Professor Mathias Heikenwälder:
ERC Consolidator Grant 2015

PD Dr. Angelika Riemer:
Ingrid zu Solms Science Award for Medicine 2015

Division
Tumor Virology

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Our Division is focused on "Anti-Tumor Virology", the objective being to develop oncolytic viruses (preferentially killing tumor cells) and viral vectors (transferring therapeutic genes into diseased (including cancer) cells). Our activities have led to the launching of the first virotherapy clinical trial in Germany, using the oncolytic parvovirus H-1PV to treat malignant gliomas. Based on virus safety and first signs of anti-tumor activity, a second clinical study of H-1PV in pancreatic cancer patients has been launched recently. Three main research axes are presently being developed:

1. Basic investigation of the interactions of oncolytic parvoviruses (PV) with host cells, in particular
   (i) cellular markers predictive of tumor responsiveness to PV treatment,
   (ii) PV determinants of host range,
   (iii) molecular pathways involved in PV oncotoxic properties,
   (iv) mechanisms of PV immunomodulating effects;
2. Preclinical assessment of the anticancer potential of PV, including
   (i) evaluation of the applicability of PV therapy to malignancies in children and adolescents,
   (ii) development of novel anticancer strategies based on second generation PV (vectors) and combination treatments,
   (iii) production of recombinant PV for the delivery of cyto- and chemokines into tumors and their microenvironment;
3. Our Virus Production & Development Unit standardizes protocols for virus application to humans, and supports trial-accompanying research.

FUTURE OUTLOOK:
Basic research will be pursued to unravel the cellular and parvoviral determinants of cell permissiveness and killing, respectively. This program is expected to contribute to identifying patients susceptible to oncolytic virus-based treatments ("customized" therapy). Furthermore, our ambition is also to understand and optimize the interplay between parvovirus oncolytic effects and host anti-tumor immune responses.
On the translational level, our work aims to broaden the range of indications for a potential H-1PV-based oncolytic viro-therapy, and to increase the oncosuppressive capacity of PV through adaptation and engineering. Furthermore, in order to prepare future clinical trials, optimal treatment strategies combining parvoviruses with different classes of antineoplastic and immuno-modulating agents will be tested, using various *in vitro* and *in vivo* models. Another focus of the Division lies on research accompanying the clinical trials of H-1 parvovirus in cancer patients. Of particular interest is the investigation of viral effects not only on the neoplastic compartment but also on the tumor microenvironment modulating anti-cancer immune responses.

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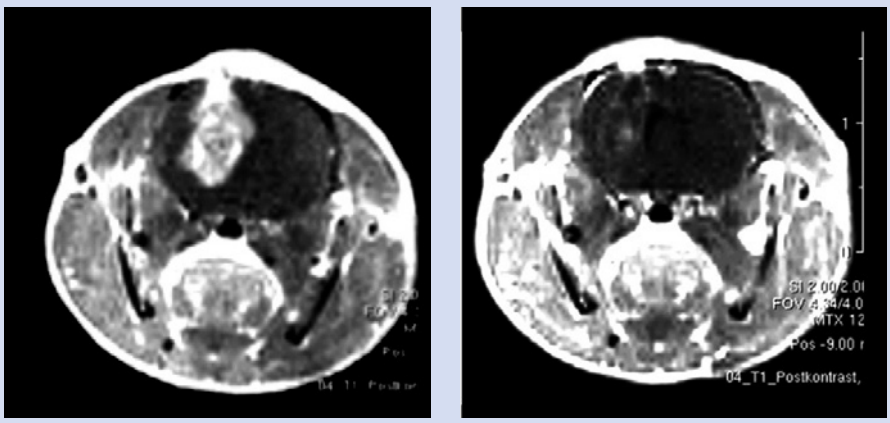
(2) Geletneky K. et al. (2015). Double-faceted mechanism of parvoviral oncosuppression. ***Curr Opin Virol,*** 13, 17-24.
(3) Li J. et al. (2013). Synergistic combination of valproic acid and oncolytic parvovirus H-1PV as a potential therapy against cervical and pancreatic carcinomas. ***EMBO Mol Med,*** 5, 1537–1555.
(4) Nüesch J.P. et al. (2012). Molecular pathways: rodent parvoviruses: mechanisms of oncolysis and prospects for clinical cancer treatment. ***Clin Cancer Res,*** 18, 3516–3523.



Treatment of an intracerebral rat glioma with parvovirus H-1 (H-1PV). MRI of a rat brain bearing a glioma, at the time of infection with H-1PV (left), and 8 days later (right), showing disappearance of the tumor after infection.

Division

Molecular Diagnostics of Oncogenic Infections

Our aim is the identification of human papillomaviruses (HPV) and other viruses and bacteria as causal factors in the pathogenesis of specific cancer entities where this has as yet not been reliably demonstrated (1). We have developed a high-throughput platform for simultaneous detection of arrays of human antibodies or nucleic acids, which we use to analyze large sample collections from collaborative epidemiological studies. We also explore biomarkers as predictors for infection-induced cancers, such as HPV mRNA patterns for early detection of cervical cancer, antibodies to HPV early proteins in oropharyngeal cancer (3), and antibody patterns to Helicobacter species in gastric and other gastrointestinal cancers. We further investigate the potential of an HPV vaccine to prevent recurrence of genital warts. Studies on cellular APOBEC3 cytidine deaminase restriction factors and their dynamic coevolution with foamy viruses (4) led to identification and characterization of APOBEC3 mutation signatures in diverse cancers. The contribution of APOBEC3 activity and genome mutations caused by APOBEC3 to infection- and inflammation-mediated oncogenesis are currently investigated.

We also study the role of lipoxygenases (LOX) in epidermal development, homeostasis and cancer (2). Current studies are aimed to decipher the implication of LOX in the pathogenesis of the inherited skin disease ichthyosis and to develop novel therapeutic approaches.

FUTURE OUTLOOK:

Several planned seroepidemiological studies will determine prevalences of multiple, predominantly oncogenic infectious agents in German and other European populations, and risk factors for these infections. A number of ongoing studies aim at analyzing genetic determinants of infection susceptibility and immune response. Infection markers with diagnostic or prognostic value will be clinically validated.

The contribution, mechanisms and control of APOBEC3-driven mutagenesis to oncogenesis will be analyzed *in vitro* and in animal models as well as patient-derived specimens. In addition, the mode of action and future exploitation of the foamy virus Bet protein as a natural and specific inhibitor of APOBEC3 as well as virus-expressed miRNAs will be studied.

Instrumentation for multiplex serology and multiplex genotyping.

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SELECTED PUBLICATIONS:

(1) Halec G. et al. (2014). Pathogenic role of the eight probably/possibly carcinogenic HPV types 26, 53, 66, 67, 68, 70, 73 and 82 in cervical cancer. ***J Pathol***, 234, 441–451.

(2) Krieg P. and Fürstenberger G. (2014). The role of lipoxygenases in epidermis. ***Biochim Biophys Acta***, 1841, 390–400.

(3) Kreimer A.R. et al. (2013). Evaluation of human papillomavirus antibodies and risk of subsequent head and neck cancer. ***J Clin Oncol***, 31, 2708–2715.

(4) Lukic D.S. et al. (2013). Identification of the feline foamy virus Bet domain SELECTED for APOBEC3 counteraction. ***Retrovirology***, 10, 76.

Division

Viral Transformation Mechanisms

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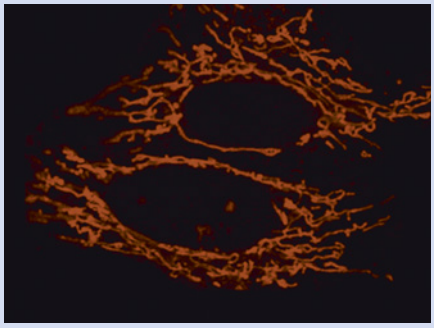
1. *Mechanisms of human papillomavirus (HPV)-induced carcinogenesis:*
   We are investigating how transcription and viral RNA splicing of high-risk HPV is regulated during the different steps towards malignant transformation, as well as epigenetic mechanisms in HPV-positive cells and their impact on viral-host interaction during persistence.
2. *Immunological surveillance:*
   We are studying the interferon/chemokine pathway to understand the innate response against viral and bacterial infections, as well as the function of individual HPV oncoproteins on the NALP3 inflammasome.
3. *A natural rodent model system for papillomavirus (PV)-induced skin cancer:*
   In this project we study the whole infection pathway of a skin tumor in molecular and serological terms. We have also developed a "virus-like particle" (VLP) based vaccine to prevent PV-induced skin lesions. This vaccine is efficient both under normal and immunocompromised conditions and will provide the basis for the clinical development of potent immunization strategies against cutaneous HPV infections and HPV-induced tumors, especially in patients awaiting organ transplantation.
4. *Virus-Cell Interactome:*
   Tumor viruses always attack central hubs to overcome intracellular surveillance. It is therefore necessary to understand these viral-host interactions using both systems biology approaches and high-throughput strategies. In particular, potential co-infections (e. g. with bacteria), their communication pathways and cross-talks are under investigation.



Mitochondria staining in primary keratinocytes (orange) (Courtesy of B. Rincon Orozco, F030).

FUTURE OUTLOOK:

1. *Metabolism and cancer:*
   We aim to determine the function of viral oncoproteins on the metabolic pathway. We have mapped the regulatory region of the LKB1 tumor suppressor gene, a master kinase that controls the intracellular energy status. This gene is found to be dysregulated in HPV-positive cells. We have also dissected the mechanism whereby tumor cells sense their own metabolism.
2. *Cellular escape mechanisms:*
   This study aims to understand the interaction of effector cells of the innate defense system with non-tumorigenic HPV-positive cells, in comparison with their tumorigenic counterparts in immunocompromised animals. We also designed experiments that allow the characterization of genes and regulatory pathways in transplanted HPV-positive cells responsible for tumor suppression.
3. *Resistance mechanisms:*
   Although most of the tumor mass can be eradicated *in vivo* and *in vitro*, there are still cells which survive. Whether these represent cancer stem cells will be studied in further detail.

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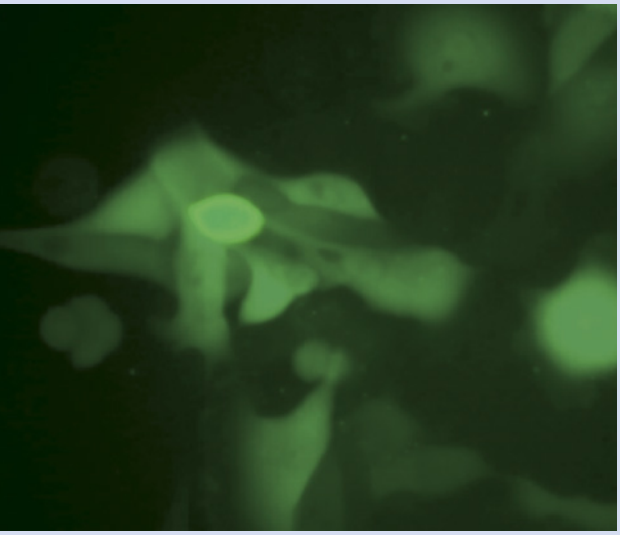
Division

Pathogenesis of Virus Associated Tumors

The Epstein-Barr virus (EBV) is etiologically linked with 2 percent of all malignant tumors worldwide. Hence, a very substantial number of cancers could be prevented by vaccination against this virus. Our research interests are focused on the molecular mechanisms that allow multiplication, infection and ultimately, malignant transformation of B cells and epithelial cells. The large size of the viral genome precludes the use of conventional cloning techniques; instead, we have developed a genetic system that allows modification of every single base pair within the viral genome. Over the years we have used this technology to construct a large panel of viral mutants that lack genes involved in multiple virus functions. More recently, we have focused our attention on viral non-coding RNAs, such as the first described v-snoRNA1 or the BHRF1 and BART microRNA cluster. We have recently identified highly pathogenic EBV strains in tumors of the nasopharynx and in gastric carcinomas. These strains induce a very strong spontaneous lytic replication in infected B cells and infect epithelial cells with high efficiency (Figure). We have also generated EBV mutants that could be potentially used as vaccines. Indeed, these mutants produce large amounts of viral DNA-free virus-like particles (VLPs) that could elicit a strong immune response, but have lost any pathogenic potential.



Primary squamous epithelial cells infected with a recombinant Epstein-Barr virus tagged with a GFP gene.

FUTURE OUTLOOK:
Future projects aim at pursuing the characterization of the various EBV strains that are found worldwide in the healthy and diseased population, and to generate vaccines to protect against highly pathogenic EBV strains.

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SELECTED PUBLICATIONS:
(1) Yu X. et al. (2015). Antigen-armed antibodies targeting B lymphoma cells effectively activate antigen-specific CD4+ T cells. ***Blood***, 125(10), 1601-1610.
(2) Tsai M.H. et al. (2013). Spontaneous lytic replication and epitheliotropism define an Epstein-Barr virus strain found in carcinomas. ***Cell Rep***, 5(2), 458-470.
(3) Feederle R. et al. (2011). A Viral microRNA cluster strongly potentiates the transforming properties of a Human Herpesvirus. ***PLoS Pathog***, 7(2): e1001294.
(4) Hutzinger R. et al. (2009). Expression and processing of a small nucleolar RNA from the Epstein-Barr virus genome. ***PLoS Pathog***, 5(8):e1000547.

Division

Virus-associated Carcinogenesis

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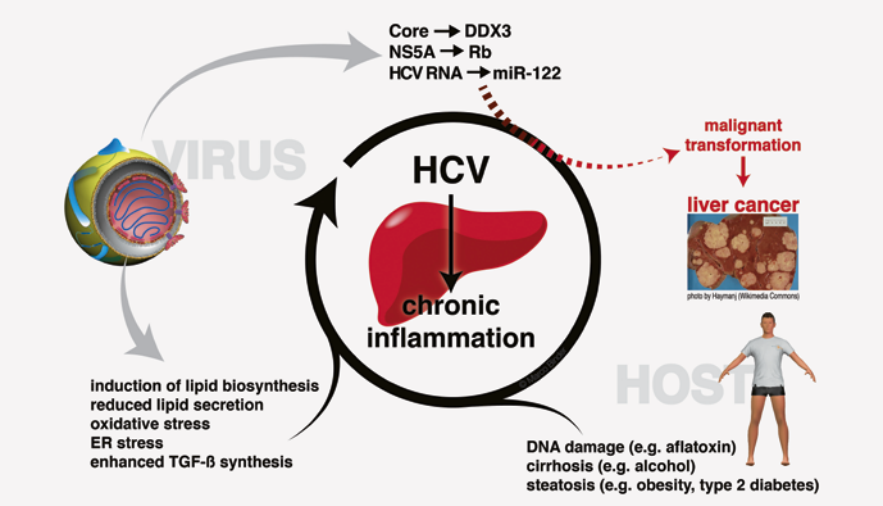
Liver cancer is a worldwide leading cause of cancer-related deaths and is to a large extent associated with chronic infections with the hepatitis B (HBV) or C virus (HCV). There is an urgent need for improved therapeutic concepts, which requires better understanding of the causative molecular processes leading to chronic viral hepatitis and ultimately hepatocellular carcinoma. One main driver of hepatitis virus-related liver cancer is the inflammation induced by chronic viral infection. It is mediated by the immune system, which attacks and destroys infected cells but does not sufficiently eliminate the virus. In addition, HBV and HCV infections causes profound alterations of host cell functions, including metabolic imbalances (e. g. fat deposition in the liver, iron overload) or activation of oncogenes. Our Division therefore focuses on analyzing the molecular and cellular mechanisms responsible for the failure of the immune response to control HBV and HCV infection, and the promotion of liver cancer resulting from this chronic infection. Currently, individual projects cover the following areas:

- Replication dynamics of HCV and control by the innate immune response
- Role of iron-regulatory networks in infection and inflammation-induced liver tumor formation
- Metabolic alterations induced by HCV and HBV

FUTURE OUTLOOK:
Our main future direction will be to integrate HCV replication dynamics with the dynamics by which viral infection induces and counteracts the immune response: this "race" determines the outcome of infection and, thus, chronicity or viral elimination. This project is based on a close collaboration with systems biologists and bioinformaticians inside and outside the DKFZ. Further on, we will focus on iron metabolism, which plays a key role in the homeostasis of hepatocytes and also appears to be involved in the HCV replication cycle and in innate immunity. We will apply expertise gained from our iron regulation analyses to study other metabolic networks that might be dysregulated in pathogen- and inflammation-induced tumor entities. Another major goal is to establish *in vivo* models for HBV, in order to study why the immune response fails to control this infection, and to determine how long-term infection induces liver cancer. In addition, we aim to establish *in vivo* systems for HCV in order to determine the molecular mechanisms by which this virus induces hepatosteatosis, which is becoming a leading cause of hepatocellular carcinoma, as well as to study the contribution of obesity to HCV-associated liver cancer.



Hepatitis C virus (HCV) infection leads to chronic liver inflammation. Together with cofactors such as obesity or alcohol consumption, this inflammation increases turn-over of hepatocytes, leading to scar tissue formation that manifests as fibrosis and liver cirrhosis. Additionally, DNA damage and oncogenic mutations can occur. Viral factors can also have direct oncogenic effects, such as interference with tumor suppressors. ©Marco Binder 2014.

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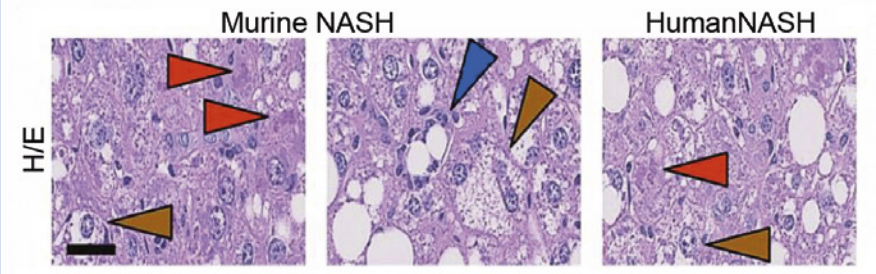
(3) Nairz M. et al. (2015). Iron regulatory proteins mediate host resistance to Salmonella Infection. ***Cell Host Microbe***, 18(2):254-261.
(4) Binder M. et al. (2013). Replication vesicles are load- and choke-points in the hepatitis C virus lifecycle. ***PLoS Pathog***, 9(8):e1003561.

Division

Chronic Inflammation and Cancer

Inflammation exists in several different flavors. Already, the time span of inflammation is a first parameter. Whereas short-lived inflammatory reactions are rather indicative of an acute, regenerative process, chronic inflammatory reactions can be deleterious causing subsequent diseases such as autoimmunity-driven tissue damage or even cancer development. In the case of liver cancer development several different chronic etiologies have been identified: chronic viral infections with Hepatitis B and C virus, chronic alcohol consumption or a high calorie diet combined with insufficient movement. Yet, no effective therapy is available that could cure liver cancer patients.
The best treatment available today is a pan-tyrosine kinase inhibitor (Sorafenib) that prolongs the lifespan of late stage patients by approximately three months. At the same time we are facing a strong rise in HCC incidence and are missing appropriate therapies. Great advances have been made to eradicate some of the etiologies of liver cancer formation (e. g. efficient treatment of HCV infections), whereas other etiologies of liver cancer – such as non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) are strongly increasing in industrializing but also developing countries and will further rise in the next years. Thus, more appropriate preclinical models as well as better immunological, genetic and molecular understanding is needed to generate new and effective therapies.
Our laboratory aims at understanding the different immune signatures of chronic inflammatory human diseases (with focus on liver diseases) and how those trigger liver damage and liver cancer using relevant mouse models – with the final aim to generate models of chronic inflammation potentially used for pre-clinical research. Thus, we focus on comparative studies of human and animal model tissues, recapitulating human disease on a histo-pathological and pathophysiological level. We engage in classical molecular biology techniques complemented with sophisticated ways to receive as much information from tissue samples through histology (e. g. light microscopy/immune fluorescence/FISH/*in situ* hybridization), *in vivo* imaging techniques (e. g. MRI) as well as FACS analyses for tissue homogenates.



CD-HFD in mice recapitulates human NASH and NASH-triggered HCC pathology. Representative H&E staining of 12-month-old CD-HFD C57BL/6 livers and human livers illustrating NASH. Accumulation of Mallory-Denk bodies (red arrowhead), ballooned hepatocytes (brown arrowhead), and satellitosis (blue arrowhead) is similar to human NASH pathology (right image). Scale bar: 50 µm. Adapted from (Wolf et al., 2014).

FUTURE OUTLOOK:
We are also interested in the systemic functional effects of pathologies and the interplay between several affected non-lymphoid tissues and the immune system. Finally, testing several therapeutic compounds in a single use but also combinatorial fashion is one of our goals employing established and stratified pre-clinical mouse models.

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SELECTED PUBLICATIONS:
(1) Lucifora J. et al. (2014). Specific and Non-hepatotoxic Degradation of Nuclear Hepatitis B Virus cccDNA. ***Science***, 343(6176), 1221-8.
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(4) Haybaeck J. et al. (2009). A lymphotoxin-driven pathway to hepatocellular carcinoma. ***Cancer Cell***, 16(4), 295-308.

Division

Episomal-Persistent DNA in Cancer and Chronic Diseases

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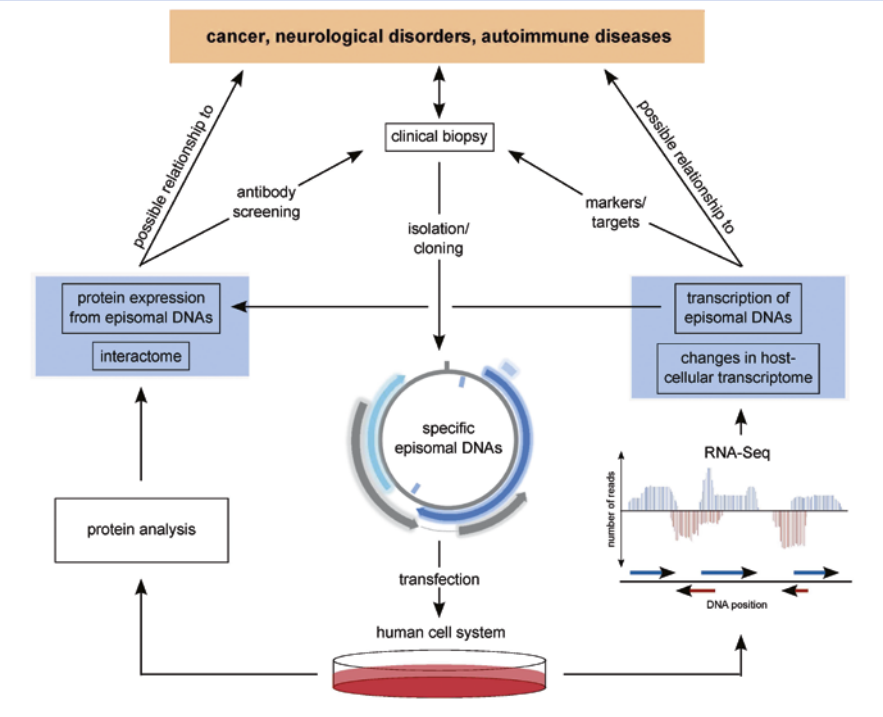
The Division of Episomal-Persistent DNA in Cancer and Chronic Diseases aims at identifying and characterizing disease-a ssociated persistent circular DNA of infectious agents in human materials. Some studies suggested an involvement of such agents in the development of chronic neurodegenerative diseases (Manuelidis, J Neurovirol 2011; 17:131–145). Besides the isolation of such DNAs, central questions remain whether, and in which way, these DNA sequences and their gene products contribute to the development of certain pathologies. Proof for a direct link between an infection with these agents and a specific disease may open new avenues for intervention (vaccination, identification of patients at risk and targeted therapy). Numerous novel episomal DNA sequences related to single-stranded circular DNA viruses have been isolated from milk, bovine sera and different human pathological biopsies (Funk et al., Genome Announc 2014; 2[4], Gunst et al., Genome Announc 2014; 2[4], Lamberto et al., Genome Announc 2014; 2[4], Whitley et al., Genome Announc 2014; 2[4]). The high degree of homology between isolates from milk, bovine sera and human tissue points to the consumption of bovine meat or dairy products as a potential route of transmission. The global epidemiology of some common human cancers (e. g. colon and breast cancer) could suggest a zoonotic origin of these conditions (zur Hausen and de Villiers, 2015).



FUTURE OUTLOOK:
The studies aim at identifying infectious agents for common human cancers (specifically colon and breast cancer) and for chronic neurological diseases (multiple sclerosis).

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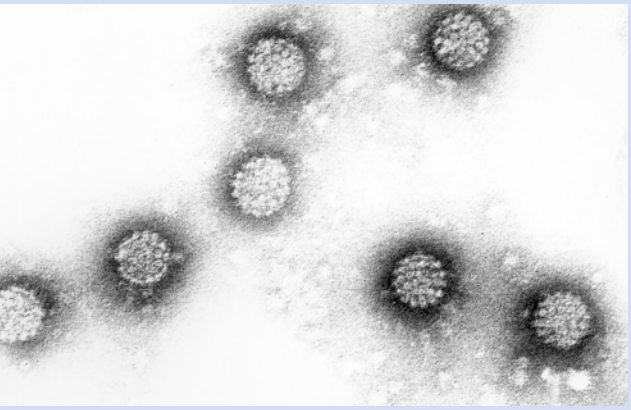
Junior Research Group

Immunotherapy and -prevention

At least 20 percent of human malignancies are caused by consequences of persistent infections. Cancers caused by infectious agents (e. g. human papillomavirus – HPV) are attractive targets for cancer vaccination approaches, as they provide the opportunity to target antigens that are immunologically non-self. Vaccination can be prophylactic, inducing antibodies that prevent infection, or therapeutic, stimulating the cellular immune system into eradicating established disease. Prophylactic immunization against HPV has become the paradigm for cancer immunoprevention. Unfortunately, current HPV



High-risk types of Human Papillomavirus (HPV) causes >5% of cancer worldwide – over 550,000 cancer cases and approximately 265,000 deaths per year.

vaccines have no therapeutic effect on existing infections. The aim of therapeutic vaccination is to stimulate the immune system into recognizing and destroying malignant cells. Cytotoxic T cells (CTL) kill infected cells after recognizing bits of viral proteins, so-called epitopes, which are presented on human leukocyte antigen (HLA) molecules on the cell surface. There are thousands of different HLA types, all presenting different epitopes. As every human being has a different set of HLA molecules, epitopes for all major HLA groups need to be defined. The overall aim of this group is to generate a therapeutic cancer vaccine against HPV-induced malignancies that is applicable to everyone, regardless of a person's HLA type. We are currently working on the precise identification of which HPV epitopes are present on tumor cells using a specialized mass spectrometry (MS) approach, and on validating them for immunogenicity and their potential to elicit functional T cell responses.

FUTURE OUTLOOK:
Nearly every sexually active individual acquires a high-risk HPV infection during their lifetime, but only 1-2 percent develop persistent infection, so there must be differences in the induction of effective immune responses. One project in the lab investigates effects of HPV on the cellular antigen processing machinery, and the resulting effects on the epitope repertoire. Future aims are to examine various vaccine delivery and adjuvant formulations. All of these studies will contribute to an optimal formulation of a therapeutic vaccine, aiming at the effective induction of adaptive immune responses in persistently HPV-infected patients. If our approach of epitope validation is successful, it may be further developed into a platform technology for other malignancies, for example in the context of tumor-specific mutation-derived neo-epitopes.

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SELECTED PUBLICATIONS:
(1) Grabowska A.K. et al. (2015). Identification of promiscuous HPV16-derived T helper cell epitopes for therapeutic HPV vaccine design. ***Int J Cancer,*** 136(1), 212-224.
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Schaller Research Group

Cellular Polarity and Viral Infection

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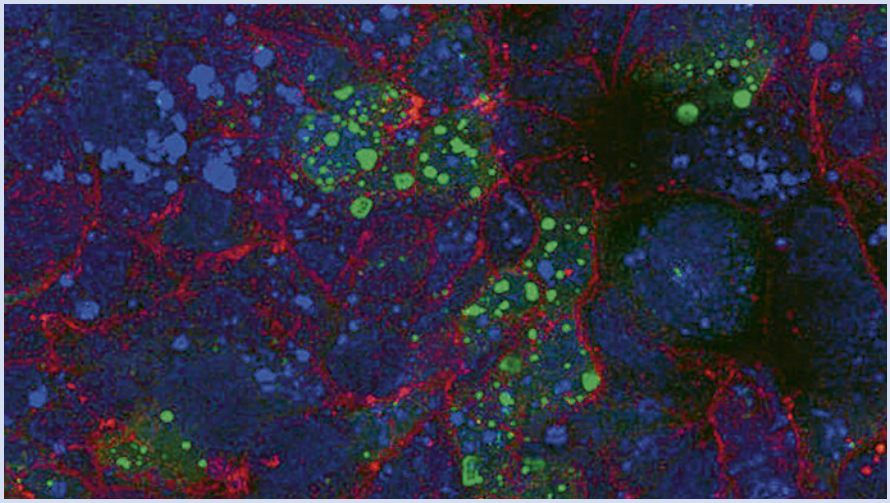
Colorectal cancer (CRC) is the third most common type of cancer worldwide. Its development is due to lifestyle choices, aging and in some cases genetic predispositions. Patients with inflammatory bowel disease (IBD) have a high risk of developing CRC. IBD has been linked with excessive inflammation in response to the microbiota. Intestinal epithelial cells (IECs) lining the surface of our gut have a very complicated dilemma. They must tolerate the presence of our commensal flora in the lumen of the gut while remaining responsive to fight enteric pathogen infection. Many studies have focused on the role that bacteria play in creating inflammation in the gut; however, viruses have been largely ignored. We believe that both enteric viruses and the anti-viral response generated by intestinal cells play an important role in controlling the inflammation and homeostasis state within the gut. In the lab we dissect the complex interactions between enteric viruses and polarized intestinal epithelial cells (IECs). Interferons (IFNs) are critical actors in innate immune defense against pathogens. Type I IFN is ubiquitous to all cells, whereas type III IFNs can only act on epithelial cells due to the restricted expression of their receptor. While looking for the molecular basis allowing the maintenance of the homeostatic state in healthy gut, we have found that similar subsets of IFN stimulated genes (ISGs) are produced upon type I and type III interferon treatment of IECs. However, the temporal expression of these genes is unique to each interferon and we believe that this functionally distinguishes both IFNs and is indispensable for the specific function of type III IFN at mucosal surfaces. We are elucidating the distinct type I vs. type III IFN signaling, in order to determine their role in the maintenance of gut homeostasis.

FUTURE OUTLOOK:
Our future perspectives are to investigate the precise functions and mode of action of both type I and type III IFNs. We are exploiting organoid mini-gut culture systems derived from human intestinal stem cells to study how human gut homeostasis is achieved and maintained. We are currently performing a systematic proteomic and genomic analysis of these mini-guts treated with either type I or type III IFNs in order to identify the key regulators that are differently functionalized by these two IFNs. Ultimately, we aim at understanding how dysregulation of this perfectly tuned immune system leads to inflammation, disease and cancer development.



Infection of polarized human intestinal cells (T84) of the enteric virus reovirus. Red: JAMA, tight junction protein and the cellular receptor for reovirus, green: Reovirus viral factories, bBlue: Cell nuclei, which show a fragmentation pattern due to apoptosis/necrotic state induced by the virus.

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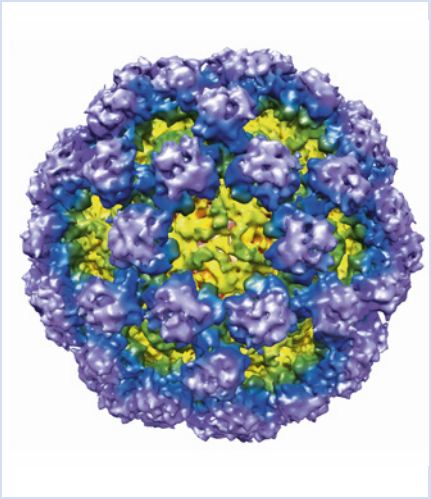
Schaller Research Group

Noroviruses

Noroviruses are the dominant cause of acute gastroenteritis around the world. Currently, there are no vaccines for noroviruses and cross-protection from future norovirus infections is uncertain, and it is not uncommon to be re-infected with a genetically similar strain. Although the disease is self-limiting, symptoms can persist for days or even weeks and transmission from person-to-person is difficult to control once the outbreak has occurred.

In closed settings such as hospitals, nursing homes, cruise ships and schools noroviruses are an enormous problem. Human noroviruses are difficult to culture, but expression of the capsid protein in a baculovirus expression system results in the self-assembly of virus-like particles (VLPs) that are morphologically and antigenically similar to the native virion. The X-ray crystal structure of the VLP shows that the capsid is divided into two domains, shell and protruding (P) domains. The P domain is further divided into P1 and P2 subdomains, with the P1 subdomain interacting with the shell and the P2 subdomain residing on the outer surface of the capsid and likely containing the determinants for receptor binding and antigenicity.

Our research group is mainly focusing on the norovirus capsid using structural biology (X-ray crystallography and cryo-EM). We are interested in the structural basis for norovirus capsid binding to a known host factor (histo-blood group antigens, HBGAs), deciphering norovirus capsid flexibility (nanobodies and monoclonal antibodies), and discovering and developing norovirus antivirals against the capsid (fucose compounds, NIH clinical collection, and drug design).



Schematic representation of a norovirus.

FUTURE OUTLOOK:

Our group will continue studies on norovirus capsid interactions with the HBGAs using X-ray crystallography. The virus capsid is an ideal target for antiviral development. At present, the HBGA binding pocket is the only known site of host interaction, but other sites on the capsid are likely to be involved in host recognition. Indeed, we recently discovered another site on the capsid that is an ideal target for developing drugs (1). We are now planning on testing several compounds in cell culture using murine norovirus as a model. We also plan to develop rapid diagnostic tests that can detect a broader range of norovirus strains in order to reduce the transmission of these viruses.

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Research Group
Mammalian Cell Cycle Control Mechanism

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Initiation and propagation of cancer is not possible without cell division (mitosis) which depends on small cellular organelles known as centrosomes. Similar to DNA replication, the centrosome is duplicated only once within a normal cell cycle. Having the correct number of centrosomes is crucial for proper chromosome segregation during cell division and for the prevention of genomic instability, a hallmark of many cancer cells. Failure to properly duplicate centrosomes results in supernumerary centrosomes, which are frequently found in tumors. The Research Group Cell Cycle Control and Carcinogenesis is studying the molecular mechanisms underlying centrosome duplication. The aim is to identify and characterize proteins that regulate this process. Our focus is placed on the key regulator of centriole duplication, the polo-like kinase Plk4.

FUTURE OUTLOOK:
Our future goal is to identify and functionally characterize novel players of the Plk4-dependent centriole duplication pathway.

For more information about our research activities, please visit our website: www.dkfz.de/en/f045/

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Research Group
Molecular Therapy of Virus-Associated Cancers

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Oncogenic types of human papillomaviruses (HPVs) belong to the most important known cancer risk factors. The Research Group Molecular Therapy of Virus-Associated Cancers studies the molecular mechanisms of viral oncogenesis, with a particular emphasis on the interplay between HPVs and the host cell metabolism. We expect that these studies will not only be informative for tumor virology but will also improve our general concepts of human cancer development. Moreover, deciphering the mechanisms of malignant cell transformation is a prerequisite for the development of innovative strategies for targeted cancer therapy.

FUTURE OUTLOOK:
Future research will analyze the interplay between the HPV oncogenes and the metabolic state of the host cell, including oxygenation and iron metabolism, and aims to identify metabolic targets for therapeutic intervention.

For more information about our research, please visit our website: www.dkfz.de/en/f065/

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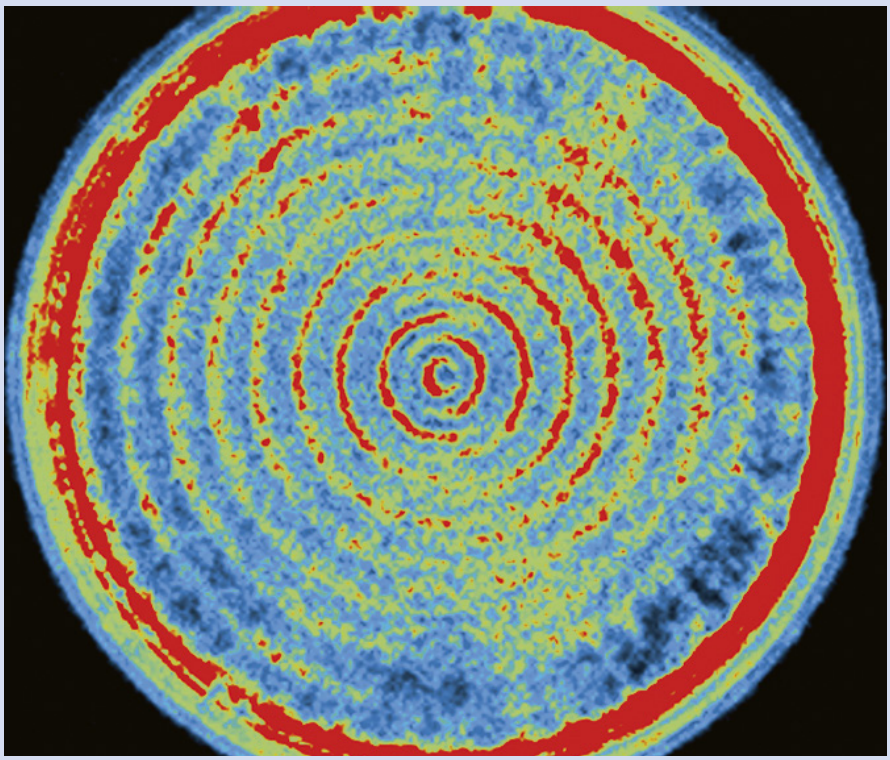
Research Group

DNA Vectors

The DNA Vector Laboratory is focused on the development and application of novel, next-generation DNA vectors for gene therapy and for the safe and persistent genetic modification of cells. These DNA vectors provide sustained transgene expression, autonomous replication and episomal maintenance without the use of toxic viral components or the risk of insertional mutagenesis. They also provide unlimited capacity allowing the unrestricted development of exquisitely designed and endogenously controlled DNA vectors. We can persistently genetically modify cells *in vitro*, *ex vivo* and *in vivo* without altering their fundamental molecular characteristics.

FUTURE OUTLOOK:
Our aim is to continue to develop our DNA vector platform to more effectively genetically modify cells with minimal molecular or biochemical impact. We are using this DNA vector platform to create a library of novel isogenic cells, to genetically modify stem cells and to treat monogenetic disease.
In an over-arching project we are also learning more about the functional capabilities and the mechanism the vector system utilises to remain episomal, to autonomously replicate and provide sustained transgene expression within a cell.



Human pancreatic adenocarcinoma cells were genetically modified with an episomally maintained DNA vector expressing Luciferase. This figure is a photograph of a growing culture of these modified cells which tend to grow as aggregates. In this picture the transgenic light they emit is captured as concentric circles with the colours representing its intensity.

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SELECTED PUBLICATIONS:
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Research for a Life without Cancer

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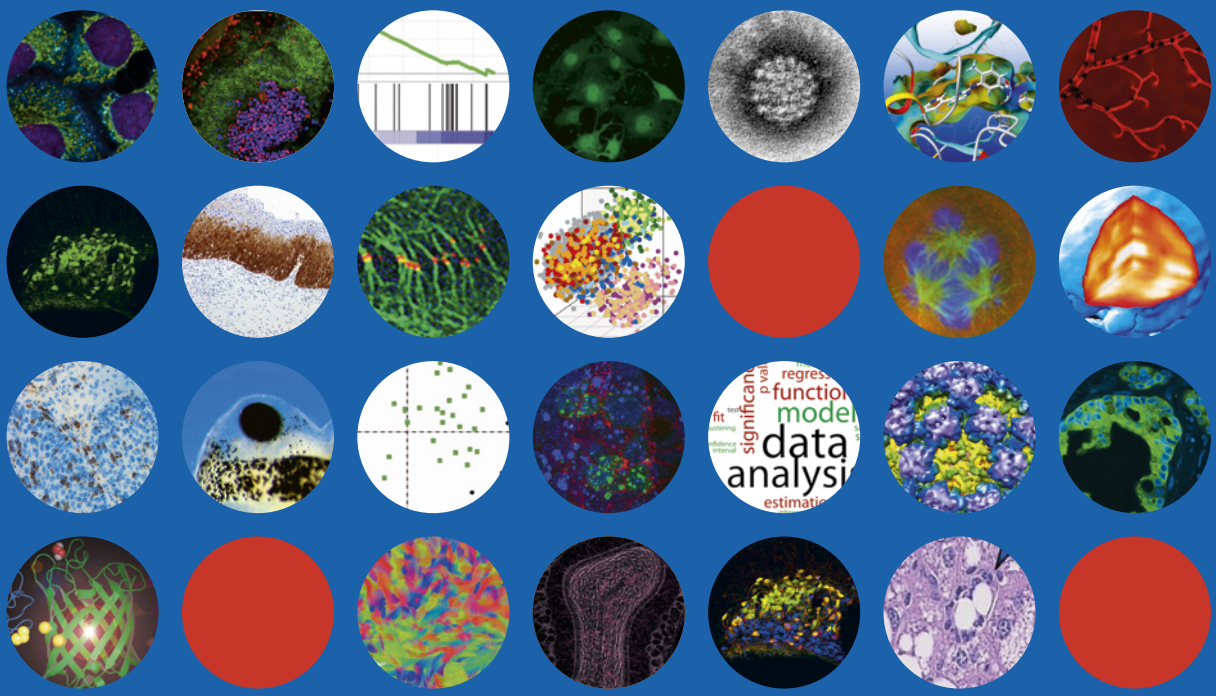

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