

Institute of Clinical and Molecular Virology

Chair of Clinical and Molecular Virology

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Research focus

- Retroviral infections
- Herpesviral infections
- Antiviral immunity

Structure of the Chair

Professorships: 4
Personnel: 106
• Doctors (of Medicine): 6
• Scientists: 13 (thereof funded externally: 9)
• Graduate students: 16

Clinical focus areas

- Serological, molecular biological, and virological diagnostics of viral infections
- Drug resistance testing
- Genotyping

Research

Despite substantial progress in our understanding of viral host cell interactions and the interplay between viruses and the immune system, there still is an unmet medical need for the prevention and therapy of persistent viruses and viruses of the respiratory tract. The research focus of the Institute therefore is to explore novel antiviral therapies and preventive measures that are based on molecular analyses of the interaction of viruses with the host cell and the immune system.

Retroviral infections

PI: Dr. A. Thoma-Kreß¹, Prof. Dr. U. Schubert², Prof. Dr. K. Überla³, Prof. Dr. T. Gramberg⁴
Both human pathogenic retroviruses, human T-cell leukemia virus (HTLV) and human immunodeficiency virus (HIV), are the subject of extensive research by the Institute.
The first research group investigates the molecular mechanisms of cell-to-cell transmission of

HTLV-1. The group developed new assays and methods to facilitate studies on viral transmission and the transport of viral proteins during cell-to-cell transmission.

The second research group investigates the role of regulatory HIV-1 proteins in the pathogenesis of HIV-1, whereby it could be shown that the HIV-1 p6 Gag protein regulates the membrane association, ubiquitination, and thus the entry of Gag into the MHC-I antigen presentation pathway. While the viral protein Vpr is involved in HIV-associated fat metabolism diseases, Vpu directs the polyubiquitination of certain host cell-receptors.

One of the questions addressed in the third research group is how intron-containing HIV-1 mRNAs are captured in the cell nucleus. A genome-wide screen using the CRISPR/Cas technology led to the identification of several spliceosome-associated proteins. The inactivation of the corresponding genes increased the cytoplasmic levels of the intron-containing genomic HIV-1 RNA up to 140-fold.

The fourth group focuses on the effect of the host restriction factors SAMHD1 and TRIM5a on the replication of HIV-1 and the retransposition of LINE-1. Using knockout mice, the group was able to show that SAMHD1 has broad antiviral activity. By blocking retrotransposition of mobile genetic elements like LINE-1, SAMHD1 also seems to contribute to genome integrity. In the field of diagnostics, the focus is on the development of phenotypic drug resistance tests for HIV-1.

Herpesviral infections

PI: Prof. Dr. M. Marschall¹, Prof. Dr. T. Stamminger² (until 12/2017), Prof. Dr. A. Ensser³, PD Dr. B. Biesinger⁴, PD Dr. F. Neipel⁵, Prof. Dr. W. Doerfler⁶

The Institute is working on various cell biological aspects of herpesvirus infections.

The first research group studies the regulatory role of protein kinases in the replication of the human cytomegalovirus (CMV) and related herpesviruses. In particular, the importance of protein kinases for the nucleo-cytoplasmic egress of viral particles has been demonstrated. A functional involvement of the CMV-encoded protein kinase pUL97 in these processes was shown, as well as their regulatory interaction with cellular cyclins. Further viral and cellular components of the nuclear egress complex were identified by the use of proteomics approaches and implicated for the first time the involvement of a cellular prolyl cis/trans isomerase, Pin1, in these processes. Particular importance had the x-ray-based resolution of the crystal structure of the

nuclear egress core heterodimer as a docking site and functional platform for the nuclear release of cytomegaloviral capsids.

The second group investigates immunocellular mechanisms that contribute to the defense against CMV infections. During the last two years, they could identify the cellular protein SPOC1 as a novel factor that mediates intrinsic immunity against CMV. Furthermore, viral effector proteins are characterized which play essential roles during CMV replication or dissemination.

In their search for antiviral restriction factors, the third group demonstrated that the centrosomal protein TRIM43 restricts herpesvirus infection by regulating nuclear lamina integrity. In a long standing cooperation with Prof. M. Lehner and Prof. W. Holter (Vienna), novel T cell based immunotherapies for CMV infections were investigated.

The fourth group investigates how oncoproteins of gamma herpesviruses are capable to transform human lymphocytes to permanent growth in culture. The viral oncoproteins interact with TNF receptor-associated factors (TRAF) to activate NF-kappaB, but also to inhibit interferon-inducing signaling pathways. Thereby, the viral oncoproteins may contribute to viral persistence.

The fifth laboratory is studying the oncogenic Kaposi sarcoma-associated herpesvirus (KSHV). The group could show for the first time that the Ephrin receptor tyrosinkinase A2 (EphA2) is an essential receptor for KSHV upon infection of endothelial and epithelial cells. In addition, integrin alpha V contributes to the infection of epithelial cells by KSHV.

The epigenetics group (6) has continued its research on the epigenetic consequences of foreign DNA or of virus particle intrusions into mammalian cells. While many questions remain, the available evidence obtained from a number of different biological systems supports the view that the genomic integration of foreign DNA or the immortalization of cells with EBV can lead to alterations in the cells' CpG methylation profiles. These findings call for a caveat towards the interpretation of data obtained from genetically manipulated cells. Herpesviruses are often the cause of severe encephalitis.

However, using unbiased Next-Generation Sequencing, a completely unexpected pathogen, Borna disease virus 1 (BoDV-1), could be detected in brain tissue of a patient with fatal encephalitis of unknown origin. This was the first evidence demonstrating that this virus, which is transmitted by shrews, is indeed pathogenic in humans.

Antiviral immunity

PI: Prof. Dr. M. Tenbusch¹, Prof. Dr. M. Mach², Prof. Dr. K. Überla³

The first research group is developing novel gene-based immunization strategies against viral respiratory tract infections. A major focus of its work is the induction of local immune responses at the mucosal entry sites of the pathogens. The group could demonstrate that adenoviral vector immunization induces very potent antigen-specific, tissue resident memory T-cells in the lung which mediate efficient protection against infections with a broad spectrum of divergent influenza A viruses as well as against the respiratory syncytial virus.

The second laboratory has continued its efforts in isolating and defining protective antibodies against CMV, using murine CMV as a model system. A number of monoclonal antibodies directed at viral envelope glycoproteins were isolated that vastly differed in their capacity to neutralize the virus *in vitro*. Interestingly, the *in vivo* capacity to protect against murine CMV infection was not directly correlated to the neutralizing activity *in vitro*. A number of non-neutralizing antibodies could be defined which had similar protective capacity as potent neutralizing antibodies.

The third research group investigates mechanisms of adaptive immunity against HIV and aims at the development of HIV vaccines. The group was able to show in a highly relevant animal model that antibodies against HIV are able to prevent the infection of the very first cells. For vaccine development, the group uses gene-based immunization methods, liposomal vaccines, nanoparticles, and virus particle vaccines. One approach is to exploit T helper cell responses induced by already approved vaccines to optimize the antibody response to the HIV Env protein. Using B- and T-cell receptor transgenic mice, the influence of particulate vaccines on the activation and differentiation of antigen-specific B cells and follicular T helper cells could also be investigated. The aim of further work is to characterize the influence of HIV infection on vaccine-induced immune responses.

Teaching

Curricular lectures and courses on infectiology and immunology for students of Medicine, Dentistry, pharmacy, and Molecular Medicine are jointly given by the Institute of Clinical and Molecular Virology and the Institute of Clinical Microbiology, Immunology, and Hygiene. In collaboration with further colleagues from the

UK Erlangen as well as from Würzburg and Nuremberg, members of the Institute engage in the interdisciplinary course on infectiology and immunology (Q4). Furthermore, the Institute of Clinical and Molecular Virology offers a series of elective and compulsory optional courses for students of the Faculty of Medicine and the Faculty of Sciences. Thus, teaching in virology extends to the B.Sc. und M.Sc. degree programs in Molecular Medicine, integrated immunology, biology, integrated life sciences and molecular sciences.

The course offerings are completed by the supervision of Bachelor's, Master's, MD, and PhD theses.

Selected publications

Bootz A, Karbach A, Spindler J, Kropff B, Reuter N, Sticht H, Winkler TH, Britt WJ, Mach M. Protective capacity of neutralizing and non-neutralizing antibodies against glycoprotein B of cytomegalovirus. *PLoS Pathog* 2017; 13(8):e1006601

Held FE, Guryev AA, Fröhlich T, Hampel F, Kahnt A, Hutterer C, Steingruber M, Bahsi H, von Bojnacic-Kninski C, Mattes DS, Foertsch TC, Nesterov-Mueller A, Marschall M, Tsogoeva SB. Facile access to potent antiviral quinazoline heterocycles with fluorescence properties via merging metal-free domino reactions. *Nat Commun* 2017; 8:15071

Elsayed H, Nabi G, McKinstry WJ, Khoo KK, Mak J, Salazar AM, Tenbusch M, Temchura V, Ueberla K. Intrastructural Help: Harnessing T Helper Cells Induced by Licensed Vaccines for Improvement of HIV Env Antibody Responses to Virus-Like Particle Vaccines. *J Virol* 2018; 92(14): e00141-18

Grosskopf AK, Ensser A, Neipel F, Jungnickl D, Schlagowski S, Desrosiers RC, Hahn AS. A conserved Eph family receptor-binding motif on the gH/gL complex of Kaposi's sarcoma-associated herpesvirus and rhesus monkey rhadinovirus. *PLoS Pathog* 2018; 14(2):e1006912

Korn K, Coras R, Bobinger T, Herzog SM, Lücking H, Stöhr R, Huttner HB, Hartmann A, Ensser A. Fatal Encephalitis Associated with Borna Disease Virus 1. *N Engl J Med* 2018; 379(14): 1375-1377

Lapiente D, Bonsmann MSG, Maaske A, Stab V, Heinecke V, Watzstedt K, Hess R, Westendorf AM, Bayer W, Ehrhardt C, Tenbusch M. IL-1 beta as mucosal vaccine adjuvant: the specific induction of tissue-resident memory T cells improves the heterosubtypic immunity against influenza A viruses. *Mucosal Immunol* 2018; 11(4): 1265-1278

International cooperations

Prof. J. Ung Jung, University of Southern California, Los Angeles: USA

Prof. W. Britt, University of Alabama, Birmingham: USA

Prof. W.D. Rawlinson, Virology, University of New South Wales, Sydney: Australia

Prof. Dr. A. Balasubramanyam, Division of Endocrinology, Baylor College of Medicine, Houston: USA

Prof. Dr. D. Burton, Scripps Research, La Jolla: USA