Institute of Clinical and Molecular Virology

Chair of Clinical and Molecular Virology

Address
Schlossgarten 4
91054 Erlangen
Phone: +49 9131 8523563
Fax: +49 9131 8522101
www.virologie.uk-erlangen.de

Director
Prof. Dr. med. Klaus Überla

Contact
Renate Hott
Phone: +49 9131 8523563
Fax: +49 9131 8522101
renate.hott@uk-erlangen.de

Research focus
- Retroviral infections
- Herpesviral infections
- Antiviral immunity

Structure of the Chair

Professorships: 4
Personnel: 132
- Doctors (of Medicine): 7
- Scientists: 17 (thereof funded externally: 13)
- Graduate students: 28

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. Specificially, the Institute focused on the following topics:

SARS-CoV-2 Infection
PI: Prof. Dr. K. Überla[1], Prof. Dr. A. Ensser[2], Prof. Dr. T. Gramberg[3], Prof. M. Marschall[4], Prof. Dr. U. Schubert[5], Prof. Dr. M. Tenbusch[6]
In response to the COVID-19 pandemic, diagnostic tests were rapidly established, and a number of research projects were initiated. In a collaborative effort with Prof Jäck, human neutralizing antibodies to SARS-CoV-2 were developed and shown to have prophylactic and therapeutic efficacy in animal models. A seroprevalence study for the hotspot Tirschenreuth was performed together with Prof. Wagner from the University of Regensburg. Recombinant mutants of SARS-CoV-2 were generated that will be important for subsequent studies on virus host interaction and pathogenesis. Several drug candidates inhibiting SARS-CoV-2 replication in cell culture were identified, and their mechanisms of action and therapeutic potential is currently explored. Additional studies aim to get hints on the role of SARS-CoV-2 mutations occurring worldwide. Using animal models, the importance of mucosal immune responses after administration of viral COVID-19 vector and mRNA vaccines is also explored.

Retroviral infections
PI: Dr. A. Thoma-Kreß[1], Prof. Dr. U. Schubert[2], Prof. Dr. K. Überla[3], Prof. Dr. T. Gramberg[4]
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 mechanisms of cell-to-cell transmission of HTLV-1.The group identified molecular details of viral transmission and found new cellular players regulating the transport of viral proteins between cells. In the long term, the group aims at developing prevention strategies against mother-to-child transmission. Beyond, the HTLV-1 group studies the regulation of viral transcription.
The second research group investigates the role of small HIV-1 proteins in the pathogenesis of HIV-1, whereby it was shown that the p6 Gag protein represents the first known viral substrate for the insulin degrading enzyme (IDE). Thereby, p6 is ~100-fold more efficiently degraded by IDE than its eponymous substrate insulin. This phenomenon is regulated by the N-terminus of p6 and is specific for the pandemic HIV-1 group M isolates.
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 effects of intrinsic host restriction factors on viral replication and mobile genetic elements . Using knockout mice, the group showed that HIV restriction factor SAMHD1 also blocks MCMV replication in vivo and is counteracted by the viral kinase. Also, the group found that the antiviral factor TRIM5α restricts and senses LINE-1 retroelements and therefore protects the integrity of the host genome. 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. Marschall[1], Prof. Dr. A. Ensser[2], PD Dr. B. Biesinger[3], PD Dr. F. Neipel[4], Prof. Dr. W. Doerfler[5]
The Institute is working on various cell biological aspects of herpesvirus infections.
The first research group studies the regulatory role of protein kinases (PKs) in the replication of human cytomegalovirus (CMV) and further herpesviruses and the utilization of PK inhibitors in antiviral therapy. PK activities play an important role in viral replication processes, such as the nuclear particle egress, interaction with the cell cycle and viral pathogenesis. A multifaceted regulatory contribution of the CMV-encoded PK pUL97, including a pUL97 interaction with cyclins, could be demonstrated. Further viral and cellular components of the nuclear egress complex (NEC) were identified by proteomics approaches and structure-function analyses led to its validation as an antiviral target. Very recently, the prototype of a NEC inhibitory small molecule could be reported.
In their search for antiviral restriction factors, the second 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 third 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 fourth laboratory is studying the oncogenic Kaposi sarcoma-associated herpesvirus (KSHV). The group could show that the Ephrin receptor tyrosinkinase A2 (EphA2) is a receptor for KSHV upon infection of endothelial and epithelial cells. In collaboration with the group of Prof. Felix Rey (Institute Pasteur) the group was able to clarify the structure of the gH/gL/EphA2 complex and experimentally identify single amino acids essential for the interaction. This knowledge is currently used to generate inhibitory antibodies.
The epigenetics group (5) has studied the worldwide rise of SARS-CoV-2 mutations. Analyses of sequences from GISAID revealed 10 frequent mutations in Covid-19 isolates up to late May. Between May to September and on to December 2020, numerous new mutations were selected, including multi-faceted variants from England, South Africa, and Brazil. Up to >50% of mutations were due to C to T transitions, likely caused by deaminases in the cellular APOBEC function. Hence, an antiviral shield seemed perverted to a mutagenic activity.
While herpesviruses are a frequent cause of encephalitis, a completely unexpected pathogen, Borna disease virus 1 (BoDV-1), could be detected by unbiased Next-Generation sequencing of brain tissue of a patient with fatal encephalitis of unknown origin, This was the first evidence demonstrating that BoDV-1, which is transmitted by shrews, is indeed pathogenic in humans.

Antiviral immunity
PI: Prof. Dr. M. Tenbusch[1], Prof. Dr. M. Mach[2],

Prof. Dr. K. Überla[3], PD Dr. V. Temchura[4]
The first research group is developing novel gene-based immunization strategies against viral respiratory tract infections and analyse the important role of local immunity at the mucosal entry site of the pathogens. Potent antigen-specific lung-resident memory T-cells induced by mucosally applied vector vaccines provide efficient protection against a broad panel of influenza A Viruses, the respiratory syncytial virus and most probably against SARS-CoV-2 as well. Furthermore, serological tests for the detection of different immunoglobulin subclasses against Influenza, RSV and SARS-CoV-2 have been established.
The second laboratory has continued its efforts in isolating and defining the mechanisms of protective antibodies against the fusion protein gB of HCMV. By utilizing a panel of virus-neutralizing gB-specific monoclonal antibodies (MAbs), it was demonstrated that syncytium formation of an intrinsically fusion-active gB/VSV-G chimera was inhibited by only a subset of neutralizing MAbs, which target a distinct antigenic domain of gB. This observation argues for differential modes of action of neutralizing anti-gB MAbs and suggests that blocking the membrane fusion function of gB could be one mechanism of antibody-mediated virus neutralization.
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. The aim of further work is to characterize the influence of HIV infection on vaccine-induced immune responses.
The fourth working group uses B- and T-cell receptor transgenic mice to investigate the influence of nano-particulate vaccine candidates and immunomodulating substances on the activation and differentiation of antigen-specific B cells and follicular T helper cells. The further goal is to characterize the applications of antiviral nano-particulate vaccines to improve antibody responses in small animal models.

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 theUK 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, amongst others as part of a structured programme within the research training grant GRK2504 "Novel antiviral approaches".

Selected publications

Deutschmann J, Schneider A, Gruska I, Vetter B, Thomas D, Kießling M, Herrmann A, Wittmann S, Schindler M, Milbradt J, Ferreirós N, Winkler TH, Wiebusch L, Gramberg T. A viral kinase counteracts in vivo restriction of murine cytomegalovirus by SAMHD1. Nat Microbiol 2019; 4:2273-228.

Donhauser N, Socher E, Millen S, Heym S, Sticht H, Thoma-Kress AK. Transfer of HTLV-1 p8 and Gag to target T-cells depends on VASP, a novel interaction partner of p8. PLoS Pathog 2020; 16(9):e1008879.

Full F, van Gent M, Sparrer KMJ, Chiang C, Zurenski MA, Scherer M, Brockmeyer NH, Heinzerling L, Stürzl M, Korn K, Stamminger T, Ensser A, Gack MU. Centrosomal protein TRIM43 restricts herpesvirus infection by regulating nuclear lamina integrity. Nat Microbiol 2019; 4:164-176.

Klessing S, Temchura V, Tannig P, Peter AS, Christensen D, Lang R, Überla K. CD4+ T cells induced by tuberculosis subunit vaccine H1 can improve the HIV-1 Env humoral response by Intrastructural Help. Vacccines (2020); 8: 604; doi:10.3390/vaccines8040604.

Lapuente D, Maier C, Irrgang P, Hübner J, Peter AS, Hoffmann M, Ensser A, Ziegler K, Winkler TH, Birkholz T, Kremer AE, Steininger P, Korn K, Neipel F, Überla K, Tenbusch M. Rapid response flow cytometric assay for the detection of antibody responses to SARS-CoV-2. Eur J Clin Microbiol Infect Dis 2020; Oct 20:1-9. doi: 10.1007/s10096-020-04072-7. Online ahead of print.

Muller YA, Häge S, Alkhashrom S, Höllriegl T, Weigert S, Dolles S, Hof K, Walzer SA, Egerer-Sieber C, Conrad M, Holst S, Lösing J, Sonntag E, Sticht H, Eichler J, Marschall M. High-resolution crystal structures of two prototypical β- and γ-herpesviral nuclear egress complexes unravel the determinants of subfamily specificity. J Biol Chem 2020; 295: 3189-3201.

International cooperations

Prof. Dr. Jan Gettemans, University of Ghent, Belgium

Prof. Felix Rey, Institute Pasteur, France

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

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

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