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Meeting Report

Viral pathogenesis and immune control

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Understanding viral structure-function relationships, interactions with host cells or the host's immune system are crucial for understanding the pathomechanisms of viral infections, modulation of immune responses, and the development of effective and preventative and therapeutic measures. The international workshop on "Viral Pathogenesis and Immune Control" organized by Thomas Hünig and Sibylle Schneider-Schaulies at the Institute for Virology and Immunobiology of the University of Würzburg from 6 to 8 June, 2002, brought together a group of leading experts in these fields. The meeting was held to honor Volker ter Meulen, who during the last four decades gained a high scientific reputation in virtually all aspects of viral pathogenesis. He received numerous prestigious awards, amongst them that of the International Society for Neurovirology in 2000.

The scientific program of the meeting started with a presentation by **Brian Mahy** (Centers for Disease Control, Atlanta). He reviewed emerging viral diseases, including immune deficiency syndrome (AIDS), first recognized in the 1980s and 1990s, and influenza virus, a continuous threat to the human population. Filoviruses, the paramyxoviruses Hendra and Nipah, and Hantaviruses highlight the increasing tendency of animal viruses to infect humans with devastating results, especially when they infect the central nervous system (CNS). Among prion diseases, transmissible spongiform encephalopathy, bovine spongiform encephalopathy (BSE), emerged in cattle in Europe and spread to a variety of species, including humans. Many more agents will probably be added to this list as ecological niches are altered through new forms of land use and global climate change. Viral determinants involved in crossing of the species barrier are as yet ill defined. Before efficient prophylactic and control measures can be established and implemented, much needs to be learned about these viruses, their host interactions, and their pathomechanisms. High throughput analyses of new agents aimed at identifying infection-related genes were presented by **Ian Lipkin**, New York. Techniques to be employed are based on differential display analyses and polymerase chain reaction (PCR) approaches with primers suitable for large-scale screening. Thereby, as yet unknown viruses are likely to be discovered. The association of these and known viruses with acute and chronic disease processes as well as their effect on the regulation of cellular genes can be evaluated. The identification of West Nile virus as causative agent of encephalitic cases in New York in 1999 by these means is a striking example of the power of these technologies. They may also be instrumental in resolving the still controversial issue whether or not Borna disease virus is a human pathogen.

The importance of understanding structure-function relationships of viral structural proteins for basic replication and pathogenesis was highlighted by **Stuart Siddell**, Bristol. After reviewing the current knowledge on the transcription/replication strategy of coronaviruses, he focused on the identification of proteolytic products of the replicase polyprotein and the role of a virus encoded 3C-like proteinase in this process. He also reported on the establishment of a reverse genetic system for coronaviruses and outlined its potential use to study viral pathogenesis or as a vector system for the expression of foreign genes. Foamy viruses (FV) deviate from all other retroviruses in various aspects, two of which were discussed by **Axel Rethwilm**, Dresden. (i) FV express their Pol protein independently from the preceeding gag reading frame, raising the question of how Pol protein is incorporated into the viral capsid. In recent experiments it was shown that Pol interacts with RNA, which is packaged by Gag protein. (ii) The interaction between the Env glycoprotein and the FV capsid is highly specific. Unprecedented in virology, the signal peptide of FV is a structural virion protein, which, with its very N-terminus, interacts with the Gag protein, facilitating the export of enveloped viral capsids. The pathway of replication occupied by FV appears to bridge the mechanisms

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by which retroviruses and hepadnaviruses replicate. Although the agent cannot be eliminated from nature, disease caused by tick-borne encephalitis virus (TBEV) can be efficiently controlled and prevented in humans. The virus contains two transmembrane proteins, E and M, and **Franz Heinz**, Vienna, presented a combination of structural, biochemical, and functional analyses of the TBEV E protein, which is the prototype of the new class II of viral fusion proteins. Liposome fusion assays with recombinant subviral particles (RSPs) demonstrated the most efficient and fastest rates of viral fusion ever seen. Lateral interactions among the E and M proteins stabilize capsidless particle and virion assembly where uncleaved M protein chaperones E through the low-pH environment of the endosomes to prevent premature conformational change. The structure suggests a model for trimer association under fusion-inducing conditions. Oligomeric, pH-dependent rearrangements of the E protein with dissociation of the subunits of the native E homodimers and subsequent reassociation into homotrimers appear crucial. Interestingly, another class II fusion protein, the Semliki Forest virus fusion protein, revealed a striking structural similarity to that of TBEV, suggesting common biological properties of these molecules. **Geoffrey Smith**, London, reviewed the phylogenetic relationships of poxviruses, which demonstrate a centrally localized urpox replicon and additional, probably host-derived, genes at the genomic termini. Based on recent data, vaccinia virus most likely originated from an equine rather than a cow ancestor. For vaccinia virus particle morphogenesis, viral proteins involved in microtubule-mediated egress of the intracellular enveloped virus (IEV) to the cell surface and thus extracellular enveloped virus (EEV) production are particularly important. Located on intracellular enveloped virus (IEV) particles, the F12L protein colocalizes with endosomal compartments and microtubules, and is absent from intracellular mature virus (IMV), cell-associated enveloped virus (CEV), or virions attached to actin tails. Deletion of F12L prevents movement of virions to the cell surface and CEV particle formation. The F12L protein defines a new stage in the morphogenic pathway and is necessary for microtubule-mediated egress of IEV particles to the cell surface.

Several presentations centered on virus–host cell interactions, with transformation being one of the most dramatic consequences. **Peter Vogt**, San Diego, started his talk by reviewing the history of probably the most famous oncogene, Myc. Mutated or virally transduced forms of Myc induce lymphoid tumors in animals, and deregulated expression of Myc is associated with numerous human cancers. To be oncogenic, Myc must dimerize with another basic helix-loop-helix leucine zipper protein, Max, and therefore, compounds that interfere with Myc/Max dimerization would be expected to control Myc activity. A fluorescence resonance energy transfer (FRET)-based system was used for screening of combinatorial chemical libraries and candidate inhibitors of Myc/Max dimerization were validated for their ability to interfere with Myc-induced oncogenic transformation in chicken embryo fibroblast cultures. These inhibitors and others to be identified by this approach might prove invaluable for therapeutic interventions. Mechanisms of viral oncogenesis were also addressed by **Kamel Khalili**, Philadelphia. The human polyomavirus, JC virus (JCV), provides an excellent model system to investigate the reciprocal interaction of the immune and nervous systems. Under immunosuppressed conditions, the virus enters a lytic cycle, causes destruction of glial cells and a fatal demyelinating disease. Similar to SV40, JCV encodes for a T antigen with transforming potential *in vitro* and *in vivo*. Thus, JCV is detectable in about 40% of clinical medulloblastoma, and mice transgenic for JCV develop cerebellar tumors. Though there are similarities between SV40 and JCV T antigens in the control of intracellular signaling pathways, JCV T antigen can also impair DNA repair in a p53-independent manner. Signaling cascades modulated by the virus include the protein kinase A and B and Wnt pathways. There is evidence for a mechanistic link of cAMP to the Wnt signaling pathway via GSK-3β and beta-catenin by the antitumor activity of A3AR agonists.

Although the transforming ability of γ-herpesviruses *in vitro* and their association with human malignancies is known, the role of the viral immunomodulatory gene products in oncogenesis are ill defined. **Bernhard Fleckenstein**, Erlangen, addressed this topic in discussing three *Herpesvirus saimiri* (HVS) proteins and their pathogenic potential. Recombinant viruses deficient for the virally encoded cyclin D analogue, however, were not attenuated when used to infect rhesus macaques. Similarly, HVS vFLIP, which provides an antiapoptotic function and thereby would be expected to promote survival of the infected cells, was not essential for viral replication, transformation, or pathogenicity. As found by recent work of his laboratory, HVS also encodes an interferon regulatory factor (v-IRF), the role of which in pathogenicity and oncogenicity will be evaluated once the appropriate recombinant virus will be available.

Viral modulation of host immunity was addressed by several speakers. The rules that govern memory T-cell differentiation are not well understood. Studies with LCMV-infected mice reported by **Rafi Ahmed**, Atlanta, revealed that after antigenic stimulation, naive CD8+ T cells become committed to dividing at least seven times and differentiating into effector and memory cells. Once the parental naive CD8+ T cell had been activated, this developmental process could not be interrupted and the daughter cells continued to divide and differentiate in the absence of further antigenic stimulation. Thus, initial antigen encounter triggers an instructive developmental program that requires interleukin (IL)-15 and

does not cease until memory CD8+ T cells have been formed. As evidenced by microarray analysis, high levels of effector gene–specific transcripts accumulate in CD8+ memory T cells, while in effector cells, production of the corresponding proteins prevails. Interestingly, reprogramming of CD8+ memory cells is complete only 60 days after antigen encounter, and at least transient absence of antigen is required for its full establishment. Persistence of antigen may disturb this developmental program. These data provide a new concept for establishment and maintenance of CD8 T cell responses in that the entire pool of CD8 memory T cells is maintained and constantly cycles at low frequency in the absence of antigenic stimulation.

The large, complex genomes of herpesviruses document the high degree of adaptation of these viruses to their hosts. Not surprisingly, the methods developed over the past 30 years to analyze herpesvirus genomes have paralleled those used to investigate the genetics of eukaryotic cells. The recent use of bacterial artificial chromosome (BAC) technology in herpesvirus genetics, reviewed by **Ulrich Koszinowksi**, Munich, has made their genomes accessible to the tools of bacterial genetics. Systems for highly efficient genetic manipulation are now established for both human (HCMV) and murine cytomegalovirus, and, for the latter, mutants have been successfully employed for the *in vitro* and *in vivo* evaluation of gene products interfering with apoptosis, major histocompatibility complex (MHC) class I presentation at multiple stages, and activation of natural killer (NK) cells mostly in a nonredundant, complementary, and cooperative fashion. With the availability of an HCMV BAC, viral genetic determinants of endothelial cell tropism in clinical isolates of HCMV can now be identified.

The influenza A virus pandemic of 1918 to 1919 resulted in an estimated 20 to 40 million deaths worldwide. Attempts have been made to link genetic variations of the hemagglutinin and neuraminidase sequences of the 1918 virus to enhanced pathogenicity. **Peter Palese**, New York, reported about the sequence of the A/Brevig Mission/1/18 (H1N1) virus nonstructural (NS) segment encoding two proteins, NS1 and nuclear export protein. The NS1 protein of influenza A viruses is a multifunctional regulatory factor involved in post-transcriptional regulation of cellular mRNA synthesis and also counteracts the cellular antiviral interferon (IFN) activity. By using the recently developed technique of generating influenza A viruses from cloned cDNAs, the hypothesis that the 1918 virus NS1 gene played a role in virulence was tested in a mouse model where 1918 NS1 viruses proved to be attenuated. Furthermore, by a recently initiated microrarray-based approach, multiple cellular gene products were found to be differentially regulated by NS1-expressing and -deficient strains. A closer analysis will lead to a deeper understanding of influenza A pathogenicity.

Human MxA protein is a member of the IFN-induced Mx protein family and an important component of the innate host defense against RNA viruses. As presented by **Otto Haller**, Freiburg, these large GTPases form high-molecular-weight oligomers *in vivo* and *in vitro*. Binding and hydrolysis of GTP induces conformational changes in MxA filaments into rings and compact helical arrays that may be essential for target recognition and antiviral activity. With La Crosse virus, MxA traps nucleocapsid proteins in cytoplasmic inclusions, which renders this protein no longer available for the generation of new virus particles. For Thogoto virus (THOV), a member of the Orthomyxoviridae, the cellular localization dictates the target for MxA-dependent inhibition: while cytoplasmic MxA interferes with nuclear import of vRNPs, this protein, when artificially targeted to the nucleus, inhibits primary viral transcription. Using a genetic approach, a novel gene product of THOV encoded by a nonspliced mRNA from segment 6 was identified. This protein acts as a type I IFN antagonist, and thus adds to the evolving common theme that evasion from interferon control is of crucial importance for viral survival and consequent pathogenicity. **Stella Knight**, London, proposed in her talk that changes in immune activity in HIV-1 infection are secondary to two aspects of the function of dendritic cells (DC). These initiate primary T-cell responses to human immunodeficiency virus (HIV) but also disseminate virus to T cells. In addition, the capacity of DC to initiate primary T-cell responses is progressively lost. She established that DC stimulate syngeneic T cells by transfer of MHC molecules to DC of the responder type. The failure of T-cell stimulation by DC in HIV infection is associated with a defect in antigen transfer to other DC, whereas DC that acquire and present antigen directly to stimulate T cells are still functional. The latter situation leaves hope that immunotherapy via DC may be still feasible. However, DC from HIV-infected individuals cluster B cells and promote antibody production, suggesting that the shift from predominantly type 1 to type 2 activity may be a consequence of changes in DC function. There is evidence that a switch in DC from production of IL-12 to IL-4 and an autocrine loop promoting further IL-4 production in DC may underly this switch in T-cell activity caused by immunosuppressive retroviruses. Treatment that pushes the DC back towards stimulating T cells, despite increased viral dissemination, may promote protective immunity.

Adriano Aguzzi, Zürich, started the session on "Viral pathogenesis in the CNS" by reviewing the current knowledge about neuroinvasion of PrP. The agent is acquired by follicular dendritic cells in germinal centers, with complement receptors and signals provided from B cells being involved. Lymphotoxin B promotes prion replication and, consequently, suppression of this cytokine is inhibitory and may provide an approach for postexposure prophylaxis. Close proximity of peripheral sympathetic

nerve endings with follicular dendritic cells (FDC) in germinal centers experimentally achieved in CXCR5-deficient mice resulted in enhanced transmission of the agent, supporting the notion that it gets access to the peripheral nerve system (PNS) in the lymph node. Aguzzi provided evidence that immunization to prions is probably feasible because mice transgenic for the heavy chain of a Prp antibody did not develop autoimmunity and efficiently restricted Prp replication in brain tissue. A protein named Doppel (Dpl) shares significant biochemical and structural homology with PrP(C), and causes neurological disease when overexpressed in specific strains of PrP(C)-deficient mouse lines. Dpl neurotoxicity is counteracted and prevented by PrP(C), but the mechanism of antagonistic PrP(C)-Dpl interaction remain elusive. In contrast to PrP(C), Dpl may be dispensable for prion disease progression and for the generation of PrP(Sc). Although its function is not yet fully understood, Dpl has already provided some answers to long-standing questions and is transforming our understanding of prion biology.

Three talks focused on pathogenic aspects of lentiviral infections of the CNS. **Rüdiger Dörries**, Mannheim, reported on microglial infection by feline immunodeficiency virus (FIV). As revealed by sequence analyses, serum derived consensus sequences of the V3 loop from the viral *env* protein *ex vivo* were highly conserved to those of the inoculum virus. Those derived from microglial cells varied considerably already 14 days post infection, suggesting very early compartimentalization of viral variants in the CNS. In microglia isolated from FIV-infected animals, viral protein expression and production of extracellular virus were not detected *ex vivo*, whereas a very low amount of viral RNA was seen by reverse transcriptase–PCR (RT-PCR) a week past onset of cultures. In coculture with mitogen-activated peripheral blood mononuclear cells (PBMC), this semilatent state is changed dramatically, and a strong virus burst occurs within a few days. Besides pick up of infectious virus by PBMC, activated, but mitomycin-treated, PBMC can switch on virus replication in the microglial cells themselves. Taken together, viral variants of FIV are most likely selected from the input virus swarm by microglia, which severely restrict virus replication unless being activated. Not being accessible by chemotherapy, nonreplicating retrovirus in microglia could be a dangerous viral reservoir, which can be driven to enhanced virus replication by contact with brain-patrolling T cells.

Neurological disease associated with HIV infection results from either primary replication of the virus alone or replication of opportunistic pathogens in the CNS. **Opendra Narayan**, Kansas, reported on the regulation of viral gene expression in rhesus macaques experimentally infected with simian-human immunodeficiency virus (SHIV) (KU-2). An early burst of replication in brain tissue was followed by a period of latency, after which virus production was resumed and disease progressed in the presence of opportunistic infections. Coadministration of *Schistosoma mansonii* eggs led to production of IL-4 production, enhanced replication, and virus production in tissue macrophages. Interestingly, IFN-γ caused enhancement of virus replication in CD4+ T cells, but curtailed it in infected macrophages. A supportive role for IL-4 in the CNS disease was suggested by the presence of IL-4 mRNA in the encephalitic brains of rhesus macaques. These studies strongly suggest that cytokines regulate the sequential phases of HIV replication in CD4 T cells and macrophages. Thus, CD4 T cells transport virus into the brain where it is acquired by macrophages. Upon opportunistic infection, viral gene expression resumes and is boosted by cytokines released into the CNS microenvironment. At the same time, down-regulation of genes essential for neuronal survival and function occurs.

Given the relevance of HIV-1 long terminal repeat (LTR) sequence variation with respect to HIV-1 replication within monocyte populations and the important role that monocyte tropism is likely to play in HIV-1 infection of the brain, **Brian Wigdahl**, Hershey, reported on sequence variation within the C/EBP sites of peripheral blood- and brain-derived LTR populations. Commonly, brain-derived LTRs, but very infrequently peripheral blood–derived LTRs, possessed a C/EBP site I configuration (6G) that leads to enhanced binding of C/EBP proteins. In addition, C/EBP site II was even more highly conserved in brain-derived HIV-1 LTR populations, but not in peripheral blood LTRs, than site I. The high degree of C/EBP site II conservation in brain-derived LTRs was likely important in LTR regulation because the clade B consensus sequence conserved at C/EBP site II recruited high amounts of C/EBP family members. Moreover, conservation of the strong C/EBP site II in brain-derived LTRs was likely due to important interactions with Tat and/or Vpr. Thus, preferential occurrence of two highly reactive C/EBP binding sites in brain-derived HIV-1 LTRs, particularly from cases with AIDS dementia, suggest that these sites play important roles in LTR-directed transcription during invasion and maintenance of HIV-1 in the CNS.

The meeting ended with a session on "Lessons to be learned from Morbilliviruses," the virus family that has been a central issue of Volker ter Meulen's research over the last four decades. Measles virus (MV), the only human pathogen of this family, is the prototype, whereas agents such as rinderpest virus (RPV), peste-des-petits ruminants (PPRV), and canine distemper virus (CDV) are of pathogenic importance in their respective host species. As **Tom Barrett**, Pirbright, pointed out in his talk, RPV, which is targeted for eradication by 2010, continues to be a matter of concern, particularly in countries with political instability, such as in the African and Asian continents, where vaccination campaigns have been difficult to pursue. As alternatives to the current live vaccine, he presented the generation of recombinant

chimeric RPV-PPRV vaccines that would allow for distinction between infected and vaccinated animals. The potency of these vaccines will have to be evaluated in field tests, and they may also serve as proof of principle for genetically defined and attenuated vaccines for other recombinant morbilliviruses. Due to advances in medical biotechnology, vaccines for preventention of more than 75 infectious diseases are being or have been developed. In his presentation, **Samuel Katz**, Durham, gave an update on the success of mass vaccination programs implemented worldwide in order to eradicate measles and compared these with similar efforts for poliovirus. Now expected to be accomplished in 2015, eradication of measles by these campaigns is still hampered by the very same factors encountered with polio, such as political instability, armed conflict, and lack of health care infrastructure and diagnostic facilities in developing countries. In industrialized countries, compliance is still a major point of concern. Indiginous transmission of measles in the Americas has been interrupted in 1993, and all cases reported since then are clearly identified as imported. He clearly argued in favor of a long-term continuation of vaccination because, even after successful eradication of measles, closely related morbilliviruses could theoretically enter into the human population. He also addressed the question of measles vaccination of HIV-infected children in whom natural measles may follow a severe course. Data available from the United States where HIV-infected children are vaccinated (unless their CD4 T cell counts are below 200/ml) indicate that measles vaccination does not induce clinical disease nor does it aggravate progression to AIDS. Seroconversion rates were slightly lower than in healthy individuals; however, seropositivity dropped markedly within a few years.

As pointed out by **Martin Billeter**, Zürich, MV might appear as a paradigm of a sloppy virus in view of the irregularly shaped polyploid virions propagating only to low titers in cell culture. Yet, MV is an extremely successful, highly contagious pathogen with great sequence stability in the field; this may be attributed, at least in part, to its extremely rigid replication/transcription machinery, similar to that of other paramyxoviruses. Recent experiments indicated not only that the RNA template is covered without any gap from end to end by nucleocapsid molecules, each contacting six nucleotides, but that also internal *cis*-acting template elements are recognized optimally only when covered in the natural hexanucleotide frame. This ribonucleoprotein particle (RNP) rigidity explains the virtual absence of RNA recombination by copy choice and hence the high genetic stability of artificially inserted genes, making MV a very suitable vector system. So far elimination of inserted genes has never been observed in dozens of constructs. Nevertheless, in the few cases where the expression of added coding sequences strongly impaired MV propagation, variants with point mutations, typically nonsense mutations interrupting the added reading frame, overgrew the population.

Bert Rima, Belfast, reviewed the remarkable progress that had been made in the understanding of subacute sclerosing panencephalitis (SSPE) in terms of molecular epidemiology and mechanisms of MV infection in the CNS. However, the site where the virus persists in the body between the acute infection and the onset of CNS symptoms is still unknown. Recombinant viral replicons that express autofluorescent reporters have been developed to address the mechanism for spread of nonbudding defective MV in the CNS, and viral and host factors involved in persistent infection. Techniques for tracing viral infection in 200-μm brain sections have demonstrated axonal spread of the virus in the mouse CNS, and transfer of virus between neuronal cells, probably by a microfusion event, at the foot plate of the process. In persistently infected hNT2 cells cultures, immunity to superinfection is almost an absolute characteristic. The persistent virus is not genetically impaired and all viral proteins are expressed, but yet the persistently infected cells do not fuse. This may relate to positional rearrangement of CD46 on the cell surface. The availability of labeled standard viruses and defective interfering (DI) particles will allow to study their mutual interference and their role in persistence to be studied with new technologies.

Stefan Niewiesk, Würzburg, presented a model for inhibition of MV vaccine-induced seroconversion by maternal antibodies in cotton rats (*Sigmodon hispidus*). Using a heterologous system with transfer of human MV-specific antibodies, it was found that MV-specific B-cell responses are suppressed to a greater degree than T-cell responses. After immunization with a recombinant vesicular stomatitis virus expressing the MV hemagglutinin (VSV-H), an immune response in the presence of maternal antibodies is induced. The success of this immunization strategy depends on the fact that MV-H is a passenger protein without function for VSV-H replication, on immunization via the respiratory mucosa, and on a residual virulence of the vector. **Jürgen Schneider-Schaulies** presented data on the receptor usage of MV strains and consequences for the cell tropism and virulence *in vivo*. Recently, CD150 (SLAM) has been identified as a receptor for all MV strains, whereas CD46 serves this function only for a fraction of MV strains, predominantly those employed as vaccines. Although both receptors are expressed by PBMC and monocyte-derived DC, wild-type and vaccine strains exhibit different tropisms for such cells. Whereas PBMC are the preferred target cell for vaccine strains, DC are very efficiently infected by MV wild-type strains or recombinant viruses bearing the wild-type H protein. *In vivo* in the cotton rat, intranasal infection by vaccine strains stays localized to the lung, whereas wild-type strains or recombinants with the wild-type hemagglutinin have the capacity to spread

and to efficiently induce immunosuppression. Thus, interaction with CD46 appears to be an important attenuation factor of MV. In the final talk of the meeting, **Sibylle Schneider-Schaulies** addressed mechanisms of MV suppression and activation of immune responses. She focused on alterations of signaling pathways in T cells that are regulated by contact with the MV F/H complex with an as yet unknown surface receptor. There, two major pathways involved in the induction of T-cell proliferation, the MAP kinase and Akt/Protein kinase B pathways, proved to be disrupted. The importance of MV interference with the latter pathway for MV-induced arrest of T cells and thereby for immunosuppression was clearly established. Interestingly, MV F/H-mediated regulation of T-cell signaling may also directly affect splicing in T cells. Recent work from her group provided compelling evidence that the H proteins of lymphotropic, but not of attenuated MV strains, can activate monocytes via Toll-like receptor 2. This finding may provide new insights into the differential ability of MV wild-type and vaccine strains to stimulate virus-specific immunity in qualitative and quantitative terms.