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New Aspects of CMV-Related Immunopathology

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In tradition of the first three meetings (Frankfurt 1997, Maastricht 1999, Bologna 2000) a small group of about 50 international scientists and clinicians came together for the Fourth Symposium to continue their discussions on the manifold new aspects of HCMV pathogenesis, diagnosis and therapy. Most of the speakers have continuously participated in these meetings since 1997. Contributions to the first two meetings were published in *Monographs in Virology* (Karger 1998) and *Intervirology* (Karger 1999) which found broad interest within the community of scientists and clinicians involved in HCMV research.

The involvement of HCMV in vascular pathology has been discussed controversially and for a long time because the underlying mechanisms have remained unclear. However, ongoing in vitro and in vivo (animal models) studies as presented during this meeting not only suggest a central role of virus-induced immunopathology but also give an impression on the molecular mechanisms involved in HCMV-mediated endothelial dysfunction/injury. These effects play a role in the establishment of vascular diseases as involved in chronic allograft rejection, atherosclerosis and restenosis. The herein presented data impressively demonstrate that endothelial dysfunction may be related to HCMV-induced modulation of the immune system, e.g. cytokines, chemokines, adhesion molecules and autoreactive antibodies (Waldman et al., Lautenschlager et al., Stassen et al.).

However, the HCMV-related pathomechanisms may profoundly differ as a function of cell type, differentiation state of the host cell, and specific tissue. For example, the molecular regulation of HCMV gene expression and
HCMV-related cellular immune responses to date are unique in retinal pigment epithelial cells derived from the immune privileged retina and may explain the smouldering character of HCMV retinitis (Scholz et al.). A better understanding of these molecular mechanisms is necessary to explain how the virus actively circumvents effector functions of the innate and adaptive host immune system (Odeberg and Söderberg Nauclér, Zimmermann et al.). Many efforts have been done to understand the molecular mechanisms involved in the establishment and maintenance of HCMV latency as well as reactivation of latent virus. From these efforts, novel ideas and concepts to develop alternative antiviral drugs arose that include the prevention of viral reactivation (Murphy et al., Wiebusch and Hagemeier, Prösch et al., Neyts and De Clercq) and the definition of new targets for antiviral compounds (Winkler).

As a novel focus of interest during the Fourth Symposium, the role of HCMV-reactive T cells in protection, pathogenesis, diagnostic and therapy of HCMV infection was elucidated. In recent years, immunologists have demonstrated that patients and healthy people have a surprisingly high number of HCMV-reactive T cells. These cells may recognise different structural as well as non-structural proteins, as known so far, from 150 to 200 putative gene products of the virus. However, only two proteins, the matrix protein pp65 and the immediate-early proteins IE1, have been identified to play a role in protective cellular immunity. An attempt was made to explain the molecular basis for immunodominance of these two proteins (Frankenberg et al.). Several questions have been addressed at this meeting to explain the putative function of the HCMV-reactive T cells with respect to pathogenesis and diagnosis. Are HCMV-reactive T cells protective or are they involved in pathogenesis? Might T cells have a predictive value for the course of infection and disease? (Hoffmeister et al., Preiser et al.). Different clinical studies are underway to answer these questions. Furthermore, adoptive immunotherapy with HCMV-specific T cells has been shown at least in a subgroup of patients to be very effective in restoring HCMV-specific immune response and in protection from severe HCMV diseases in allogeneic bone marrow transplant recipients and may open an attractive approach to the currently available antiviral therapy (Einsele).

There was a bright consensus that more effective prevention of HCMV infection and disease needs alternative drugs which are able to block HCMV replication at the immediate early phase of replication, to hold the virus in its latent stage and to compensate the increasing problems of drug resistance against nucleoside analogs. New potential antivirals were demonstrated during the meeting (Neyts and De Clercq, Michel et al., Prösch et al.). Beside development of new antiviral drugs, the role of immunoprophylaxis may generally be underestimated. Therefore, one intriguing topic refers to new trends in
anti-HCMV vaccine development, especially in light to prevent congenitally transmitted HCMV infection (Hamprecht et al., Meric and Cadoz).

The meeting was made possible by the sponsors who have been listed separately. On behalf of the participants, the organizers sincerely express their gratitude and hope that the fruitful collaboration between biomedical science and industry will help to limit the risk of HCMV infection and disease.
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