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Plenary Session 7

Viral vectors/Viral latency (II)/Antiretroviral therapeutics

Chairpersons: L. Cosby (Belfast, UK)
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HSV1: a virus for tumor lysis and a vector for functional genomics

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Features of the life cycle and genomic structure of HSV1 provide an ideal starting point for the engineering of: 1) tumor-selective recombinant mutants, and 2) vectors for delivery of entire genomic loci into cells. For the first application, we have engineered HSV mutants that target defects in the p16 tumor suppressor pathway, thereby allowing selective replication in tumor vs. normal cells. Tumor cell killing by such mutants can be combined with delivery of additional anti-cancer cDNAs to provide multimodal therapy. However, hyperacute and acute immune reactions may limit the efficacy of viral oncolysis. Avenues to overcome such limitations will be discussed. For the second application, we have generated a "helper-free" packaging method that allows us to convert any bacterial artificial chromosome (BAC) containing human genomic loci into an infectious virion particle (iBAC). The iBAC method thus allows us delivery of complex genomic sequences into cultured and primary cells. For example, iBACs containing the genomic loci for the LDL receptor, for HPRT and for the CDKN2 region can be successfully expressed in cells. This method should thus allow investigations into the complexity of the human genome.

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Neuropathogenesis of Japanese encephalitis virus (JEV)

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JEV distributes Asian monsoon areas. The distribution is gradualy expanding recently and more than 35,000 cases are reported every year. JE is caused serious encephalitis by the virus replication in central nervous system (CNS). In the CNS, JEV can replicate only in neurons. We analysed this strict neurotropism of JEV.

We demonstrated the nurotropism of JEV was dependent on the degree of neuronal maturity. A study of the kinetics of JEV infection in the developing rat brain disclosed that JEV antigens disappeared in a particular pattern, i.e., from the deeper layers to the upper layers of the motor cortex, which paralleled neuronal maturation in the cortex. The 15-day-old rats, which were resistant to JEV infection, received intracerebral transplants of neurons taken from 19-day embryos. When these animals were infected with JEV after transplantation, viral antigens were detected only in the embryonal neurons soon after transplantation. These results were confirmed by primary neuronal cell culture analysises. And it was demonstrated that the initial specific binding of JEV to the neurons was one of the reasons for the neurotropism of JEV. We could demonstrate that the E protein which was receptor binding protein of JEV was one of the entities on the neurotropism of JEV by sequence analysis of attenuated virus genomes.

Most susceptible neurons in the CNS was located in substantia nigra. According this finding, we could develop animal models which showed parkinsonism. These models showed serious falling off of dopamine neurons in the substantia nigra by JEV infection.

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The brain in the era of HAART

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The detrimental effects of HIV on the brain are now well recognised. The brain is a major target for infection by HIV which is associated with a range of inflammatory disorders, synaptic and dendritic damage and neuronal loss. Clinically this constellation of pathological changes is associated with varying degrees of cognitive impairment, which previously carried a poor prognosis. However, following the introduction of highly active antiretroviral therapy (HAART) in 1996 there has been a significant reduction in mortality and a fall in the incidence of HIV associated dementia. Currently it is becoming increasingly recognised that despite long term successful treatment with HAART some individuals have persistent subtle cognitive impairments. This indicates that viral replication and neuropathological changes may still be occurring in these individuals, but clarifying this situation is difficult as mortality is still low and few brains are available for neuropathological assessment. Thus, we now exist in an era in that we are unsure of the long-term consequences for brain function of both chronic infection with HIV and extended administration of antiretroviral therapy.

In this presentation I will review our current knowledge of a number areas, including: (1) is the brain still a significant site of infection in individuals treated with HAART; (2) what is the emerging picture of brain pathology in HAART; (3) which HAART regimes work effectively in brain tissue; and (4) should we be developing brain directed therapy to ensure its long-term protection.

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Antiretroviral therapeutics

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An overview will be given of the classic groups of nucleoside analogues, protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTIs). The new classes of anti-HIV drugs: entry inhibitors, integrase inhibitors and the second generation of NNRTIs will also be covered.

NNRTIs are powerful anti-HIV agents, but resistance is common. One of the new compounds in this group is TMC 125; studies with this drug will be discussed. Entry inhibitors are compounds that can inhibit the co-receptors for HIV CCR5 an CXCR4. Data of the compound SCH-C will be discussed. Integrase is the enzyme that inserts HIV's proviral DNA into the host cell chromosome. The compound called S-1360 inhibits HIV integrase. Data will be shown. The presentation on antiretroviral therapeutics will be focussed on CNS-aspects of the drugs: CSF pharmacokinetic data, efficacy in HIV-dementia, CSF viral load data and possible CNS side effects.

Several (US and European) guidelines for antiretroviral treatment strategies and data on structured treatment interruptions (STI), including neurological consequences, will be summarized.