Oral presentations

C-1  Antiviral activity of acyclic and cyclic nucleoside phosphonates
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In collaboration with Prof. Anthonin Holý (Nature Rev. Drug Discovery, 2005; 4: 928–940), I have discovered the antiviral activity of a series of acyclic nucleoside phosphonates, which have been approved for medical use and are now worldwide available for the treatment of herpesvirus (i.e. cytomegalovirus), papillomavirus, adenosivirus, poxivirus infections [(S)-1-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine, HPMPC, cidofovir, Vistide®], hepadnavirus (hepatitis B virus) infections [bis(pivaloyloxymethyl) ester of 9-(2-phosphonylmethoxyethyl)adenine, bis(POM)PMEA, adefovir dipivoxil, Hepsera®], and human immunodeficiency virus (HIV) infections (i.e. AIDS) [bis(isopropoxycarbonyloxymethyl) ester of (R)-9-(2-phosphonylmethoxypropyl)adenine, bis(POC)PMPA, tenofovir disoproxil fumarate (TDF), Viread®]. TDF has also been marketed, in combination with emtricitabine, in a single once-a-day pill (Truvada®), and in combination with emtricitabine and efavirenz, also in a single once-a-day pill (Atripla®) for the treatment of HIV infections. Viread®, Truvada® and Atripla® may also be considered for prophylactic use, for preventing HIV infections, irrespective of the route of transmission (parenteral, sexual or perinatal). Moreover, Viread® has recently been formally approved for the treatment of chronic hepatitis B. In addition to these acyclic nucleoside phosphonates, other acyclic and cyclic nucleoside phosphonates have recently been described: 2,4-diamino-6-(R)-(3-hydroxy-2-(phosphonylmethoxy)propoxy)pyrimidine [(R)-HPMPO-DAPy], 2,4-diamino-6-(2-phosphonylmethoxyethyl)adenine (PMEOA-DAPy), 2,4-diamino-6-(2-(phosphonylmethoxy)propyl)adenine (PMEPO-DAPy), (S)-1-(3-hydroxy-2-phosphonylmethoxypropyl)-5-aza-cytosine (HPMP-5-azaC), cyclic HPMP and cyclic HPMP-5-azaC and the octadecyloxyethyl (ODE) and hexadecylphosphonylmethoxypropyl)-5-aza-cytosine (HPMP-5-azaC), cyclic HPMPC and the ethylalaninyl amidate phenol prodrug of phosphonomethoxy-2′-fluoro-2′,3′-dideoxy-didehydro-adenosine, and the deoxy/threosyl nucleoside phosphonates PMDTA and PMDTT.

C-2  Insight into influenza A(H1N1)
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Abstract not available at time of printing.

C-3  Diagnosis and monitoring of adenosivirus infections in immunocompromised patients
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Adenosivirus infections in immunocompromised hosts are characterized by a number of special properties, in comparison to other opportunistic infections. These include: 1. the propensity to infect younger age groups, although not exclusively; 2. the heterogeneity of these viruses, as the human adenoiviridae family consists of at least six genera and more than fifty viruses; 3. the absence of therapeutic options of proven efficacy, although cidofovir appears capable of an inhibitory effect with clinical relevance.

The diagnosis of adenosivirus infection in immunocompromised hosts nowadays relies mainly on the quantitative detection of viral DNA in blood plasma. Adenosviruses in immunocompromised hosts typically are first detectable in feaces, which is most likely related to viral reactivation in tonsillar or other gut-related lymphoid tissues. Clinically relevant infections develop when viral dissemination occurs. For this reason, monitoring of plasma viral DNA is a sensitive early marker of this complication. Typically, this infection can give rise to extremely high viral loads, of up to 1012 copies/ml, which are almost invariably associated with a fatal course. In disseminated adenosivirus infections several organs may be involved, most notably liver, lungs and brain. Initiation of antiviral therapy with cidofovir in early stages, employing a preemptive strategy, is often advocated to prevent such lifethreatening complications.

The occurrence of serious adenosivirus-related disease is mainly limited to hematopoietic stem cell transplant recipients of younger age groups. It has been shown that children harbor larger amounts of adenosiviruses in tonsillar and adenoid tissues. In this patient category, the frequency of this complication is widely variable, although generally considered to be increasing in recent years. Without specific diagnostic awareness, the condition may even be overlooked. Generally, there appears to be insufficient attention to the particular feature of the wide heterogeneity of adenosiviruses, even within a single patient, where multiple and sequential infections by different serotypes are known to occur.

C-4  The role of hepatitis B virus surface proteins in immune protection and escape – Occult hepatitis B virus infections in vaccinated and non-vaccinated blood donors
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Screening of blood donors for HBsAg and anti-HBc has greatly reduced the risk of transmitting HBV. The remaining risk can be further reduced by sensitive nucleic acid amplification techniques (NAT) for HBV DNA. American Red Cross has tested 3.7 million donations with Ultrio NAT (detection limit 166 IU/ml). The NAT yield was 3−5 times higher than expected. Surprisingly, 6 of the 9 donors were vaccinated against HBV and had low levels of anti-HBs (3–100 IU/L). Thus, the yield of NAT only positive donors was higher in vaccinated (1:270,956) than in unvaccinated donors (1:689,707). None of the vaccinated donors developed ALT elevations, but 2 unvaccinated did.

The preS/S DNA sequences were amplified, cloned and several clones sequenced. The vaccinated donors with protective levels of anti-HBs were expected. Surprisingly, 6 of the 9 donors were vaccinated against HBV and had low levels of anti-HBs (3–100 IU/L). Thus, the yield of NAT only positive donors was higher in vaccinated (1:270,956) than in unvaccinated donors (1:689,707). None of the vaccinated donors developed ALT elevations, but 2 unvaccinated did.

The preS/S DNA sequences were amplified, cloned and several clones sequenced. The vaccinated donors with protective levels of anti-HBs (>10 IU/L) were infected with genotypes B2, C2, 2x D and F1, while donors with less or no anti-HBs were infected with genotype A2 which is predominant in the USA and the vaccine genotype. The HBV/genotypes B2, D and F1 isolated from vaccinated donors were essentially wildtype, whereas quasispecies and escape mutations (K122E, T143A and G145R) were found in the A2 and C2 strains.

Conclusions: (i) Low anti-HBs levels induced by vaccination protect against hepatitis B and chronic infection, but favor occult infections.
(ii) The genotype A2 vaccine protects better against A2 than against other genotypes. (iii) By favoring HBsAg negative HBV infections, HB vaccine may possibly reduce the viral safety of blood donations, unless donors are also screened for HBV DNA with very sensitive assays.

C-5
Emerging viral infections – Crimean-Congo haemorrhagic fever in Turkey

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Crimean-Congo Hemorrhagic Fever (CCHF) was first detected in 2002 in Turkey. Between 2002 and 2009 nearly 4000 cases were detected, and 5% of the cases died. CCHF is a fatal viral infection described in about 30 countries, with the most extensive geographic distribution among the medically significant tickborne viruses. Humans become infected through the bites of ticks, by contact with a patient with CCHF during the acute phase of infection, or by contact with blood or tissues from viremic livestock. The occurrence of CCHF closely approaches the known world distribution of Hyalomma spp. ticks. Besides the climate change, biotic changes have significant role in description of the epidemiology of the infection. The clinical features show common dramatic progress characterized by hemorrhage, myalgia, and fever. The levels of liver enzymes, creatinine phosphokinase, and lactate dehydrogenase are elevated, bleeding markers are elongated. In pathogenesis, infection of the endothelium plays a major role. Besides the direct infection of endothelium, indirect damage by viral or virus mediated host-derived soluble factors that cause endothelial activations and dysfunction occur. In diagnosis, enzyme linked immunosassay and real-time reverse transcription-polymerase chain reaction are used. Early diagnosis is critical for the patient and the potential nosocomial infections. Supportive therapy is the essential part of the case management. Ribavirin was suggested as a beneficial, particularly at the early phase of the infection. The health care workers are under serious risk of transmission of the infection, particularly during the follow-up of the patients with hemorrhages from the nose, mouth, gums, vagina, and injection sites. Simple barrier precautions were reported to be effective.

Keynote lectures

K-I
Clinical virology of Rotavirus infection

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Rotavirus belongs to the genus Rotavirus, family Reoviridae, it contains double stranded linear RNA genome divided into 11 segments. Rotavirus is non encapsulated triple-layered particle. The middle layer is formed by inner capsid protein VP6, which serves as group and subgroup specific antigen. The external capsid comprised of two proteins, VP4, a protease sensitive protein and VP7, a glycoprotein. The NSP4 is an important non structural protein and serves as a viral enterotoxin. Rotaviruses are classified into seven antigenically distinct groups, A–G. Groups A, B and C are associated with human disease. Globally, group A rotaviruses are the major cause of diarrhea in children, responsible for an estimated 350,000 to 710,000 deaths each year. About 85% of these deaths occur in the developing countries. Group B and C rotaviruses infect mostly adults and older children and can cause small outbreaks or sporadic cases. Reports from several countries demonstrated that group B and C rotaviruses are also distributed widely. Several reports have been shown the association of group A rotavirus with extra-gastrointestinal infections particularly encephalopathy. Group A rotavirus infections are mainly caused by genotypes G1–G4, G9 and G12 rotaviruses. Currently two vaccines are available for rotavirus, a significant decrease of severe rotavirus infection was observed after vaccination. In Brazil vaccination possibly influenced the serotype distribution of circulating rotaviruses. Studies demonstrated that animal rotavirus or animal-human reassortant rotaviruses can cause human infection. Proper diagnosis of rotavirus infections and its identity is very important from the public health perspective.

K-II
Role of viruses in transplant recipients

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Patients after solid organ or stem cell transplantation are, in general, undergoing life long immunosuppressive therapy with different drugs, limiting also the immune response of the host against virus infections. Especially latent present but not highly pathogenic viruses as herpesviruses and polyomaviruses may under such immunosuppressive conditions start to initiate substantial replication and may lead to severe and potentially lethal disease. Primary or re-infection with such viruses after transplantation may be an even more severe threat.

Since many years the optimal strategy against virus infection or reactivation is evaluated and today there are some strategies to deal with posttransplant virus infections, which are of course dependent from the virus and the transplanted organ. These strategies include aspects of the antiviral treatment as prophylaxis, preemptive antiviral treatment, use of specific immunosuppressants, which also have antiviral functions as m-TOR inhibitors, or the use of long term antiviral prophylaxis for one year or even longer.

The viral diagnostic investigations are highly important in the post transplantation follow up and for guidance of therapy. The rapid and extremely sensitive diagnosis of infection contributes to early detection of ongoing virus replication and the evaluation of clinically significant virus load levels in different clinical materials decides about the initiation of antiviral treatment in the individual patient.

Improved diagnostic tools and antiviral therapeutic options together have led to a substantial decrease of posttransplant viral disease. So the aspect of the significance of virus replication in the transplanted host has changed within the last time and is now focussed increasingly onto the question of how subclinical virus replication does influence the long term function of the transplanted organs.

K-III
Epidemiology of delta hepatitis and use of laboratory tools in the management of patients

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Delta hepatitis leads to acute and chronic liver disease in humans. The causative agent, the hepatitis delta virus (HDV), is a defective virus which leads to hepatitis in humans in the presence of the hepatitis B virus (HBV). The association of both viruses in the human condition either occurs as co-infection of hepatitis B and D viruses or as superinfection with HDV of patients who are carriers of the hepatitis B virus (2). Co-infection causes acute hepatitis. Most cases resemble a typical self limited hepatitis that is clinically and histologically indistinguishable from hepatitis B or other types of viral hepatitis. However, acute HDV infection tends to aggravate the course of the acute HBV infection and is more likely to lead to fulminant hepatitis. But most often it resolves with complete recovery, as typically observed in acute hepatitis B. The rate of chronicity following co-infection is very low (<5%) and similar to that of HBV infection alone. Superinfection with HDV leads to chronic hepatitis in the vast majority (90%) of cases. Only rarely does HDV superinfection result in the clearance of both HDV and HBV. Chronic delta hepatitis represents the most severe form of chronic viral hepatitis. Although there are chronic delta hepatitis cases with a benign course and inactive disease, chronic delta hepatitis, in general, leads to more serious disease compared to chronic hepatitis B and chronic hepatitis C, with an accelerated course and early decompensation. Furthermore, chronic delta hepatitis may be an additional risk factor for the development of hepatocellular carcinoma (HCC).

K-IV
Molecular viral diagnostics

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