Summary of the 10th International Conference on Human Herpesviruses-6 and -7 (HHV-6A, -6B, and HHV-7)

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Funding information 
National Institute of Allergy and Infectious Diseases, Grant number: R13AI131614; HHV-6 Foundation

1 INTRODUCTION

The 10th International Conference on Human herpesviruses-6 and -7 (HHV-6A, HHV-6B, and HHV-7) was held at the Freie Universität, Berlin, Germany from July 23-26, 2017. It attracted more than 130 basic, translational and clinical scientists from 19 countries. Important new information was presented regarding: the biology of HHV-6A and -6B; the biology and epidemiology of inherited chromosomally integrated HHV-6A and -6B; improved diagnostic tests; animal models for and animal viruses with similarities to HHV-6A, -6B, and -7; established and possible disease associations; and new treatment strategies. Here, we summarize work presented at the meeting that is of particular interest.

KEYWORDS 
herpesvirus, human herpesvirus-6, human herpesvirus-7

2 CHROMOSOMAL INTEGRATION OF HHV-6A AND -6B, AND INHERITED CHROMOSOMALLY INTEGRATED HHV-6A AND -6B

HHV-6A and -6B (and probably HHV-7) can integrate their genomes into the host telomeres of host chromosomes in proximity to the subtelomeric region. Telomeric repeats present at the ends of the viral DNA play an important role in the integration process. The integrated virus can remain silent or can reactivate, indicating that integration represents a mechanism by which these viruses might achieve latency. While both viruses readily integrate in latently infected cell in vitro, no latently infected cells could be isolated from humans to confirm the state of HHV-6 genomes during latency. Therefore, we cannot exclude that the virus genome could also be maintained as an episome as described for other human herpesviruses.

Over many millennia, both HHV-6A and -6B have independently integrated into the chromosomes of germline cells. As a consequence, about 1% of the human race has inherited the entire viral genome from a parental germ cell. This phenomenon is termed inherited chromosomally integrated HHV-6 (iciHHV-6). In such individuals, the viral genome is present in every cell of the offspring.

2.1 The biology of chromosomal integration (abstracts 1-1, 1-2, 1-4, 1-5, 2-1, 2-4)

Following integration, expression of viral genes is controlled in part by CpG methylation. Preliminary studies found a high level of methylation...
of certain genes—for example, 87-95% methylation of the U2 gene which encodes a tegument protein. Methylation patterns were quite consistent across most cell lines examined. Upon serial passaging of these cell lines in culture, there tended to be a reduction in methylation. A second report found that repressive histone marks (particularly heterochromatin mark H3K27me and the histone variant H3.3), and not active marks, are associated with HHV-6A and -6B latency. This was not only observed in cell lines infected in vitro but also in cell lines derived from iciHHV-6 patients.

Current data suggest that HHV-6A and -6B integration occurs via homology-directed recombination. However, the putative U94 recombinase encoded by HHV-6A and -6B was recently shown to be dispensable for integration. This suggested that other viral and/or cellular factors facilitate virus integration, even in the absence of U94. Analysis of the cellular recombination pathways and other viral proteins revealed that the integration mechanisms are more complex and multifactorial. Intriguingly, inhibition of single-strand annealing (SSA) and alternative end-joining (ALT-EJ) impaired HHV-6A and -6B integration, suggesting that these pathways are involved in the integration process.

In addition, evidence was presented that the immediate early protein 1 (IE1) of HHV-6A and -6B and promyelocytic leukemia (PML) protein co-localize at telomeres. Both proteins seem to encourage virus integration, although PML protein is not essential for integration.

Complete sequence data from several strains of integrated HHV-6B were found to be completely identical between individuals. These sequences were identical to viruses circulating in pediatric patients with active infection, suggesting that in iciHHV-6 can reactivate from the integrated state resulting in an active infection.

### 2.2 Inherited chromosomally integrated HHV-6 (iciHHV-6) (abstracts 1-3, 1-11)

Investigators studied the prevalence of iciHHV-6 in two large populations in the United Kingdom. The prevalence was about 2.5% in Scotland and about 1% in England. The prevalence therefore appears to be affected by the Scotland/England heritage of the individuals. Within England, there was a north-south gradient, with higher prevalence in the north. About 80% of the iciHHV-6 individuals had HHV-6B. Most of them had the virus genome in chromosome 9q (33%) and 17p (22%). In almost 50% of people with iciHHV-6A, integration was present in chromosome 17p. Two large studies previously have reported that people born with iciHHV-6 have a higher risk of angina pectoris later in life. At the Conference, one group reported that primary endothelial cells from the umbilical cord blood of newborns with iciHHV-6 spontaneously expressed HHV-6A transcripts.

### 3 Host-cell interaction

#### 3.1 Cellular receptors (abstracts 3-1, 3-2, 3-3, 3-4, 3-5)

Although understanding is incomplete, the mechanisms of cell entry by HHV-6A and -6B are becoming much clearer. The HHV-6A envelope glycoprotein gH/gL/gQ1/gQ2 complex binds to human CD46 expressed on almost all cell types. Investigators presented data demonstrating that the binding affinity varies between different isoforms of CD46 and that there are possibly other alternative, so far unidentified, receptors.

HHV-6B envelope glycoprotein gH/gL/gQ1/gQ2 complex primarily uses the CD134 receptor to infect human cells. The binding of the complex to CD134 is necessary for the cell-cell fusion that follows infection. Some components of the gH/gL/gQ1/gQ2 were interchangeable between HHV-6B and HHV-6A, while others were not.

### 3.2 Lytic versus latent infection (abstract 3-4)

Nuclear domain 10 (ND10) is a cellular complex that possesses antiviral activity. Several human herpesviruses can interact with ND10 to subvert its antiviral functions and establish successful lytic infection; however, it remained unclear whether this is also true for HHV-6A and -6B. Investigators reported that knocking down the ND10 complex resulted in a significant increase in lytic replication of HHV-6A. Thereby, the cellular ND10 complex appears to play an important role in the decision between lytic and latent HHV-6A infection.

### 4 Innate and acquired immunity

#### 4.1 T cell and NK cell responses to HHV-6 infection (abstracts 4-1, 4-2, 4-3, 4-4, 5-2)

Most adults are chronically infected with HHV-6B, and many with -6A. In people latently infected with HHV-6A and -6B, it was shown that only 0.01% of all T cells are responding to viral epitopes. Most are CD4+ T cells. These rare circulating HHV-6B-specific CD4+ T cells can be greatly enriched by sorting for multiple specific activation markers. Several groups identified several hundred viral epitopes that are recognized by CD4+ and CD8+ cells. The majority of the epitopes are only recognized in some individuals. However, some epitopes are targeted in many individuals, and recognize the envelope glycoproteins gB, gH, and gQ, the tegument proteins U11 and U14, and the immediate early protein IE1 (U90).

NK cell activation in response to HHV-6A and -6B and HHV-7 relies on central signaling molecules of the STING-STAT6 pathway, an important arm of the innate immune response. All three of these viruses were capable of infecting NK cells, particularly HHV-6A. Infection with HHV-6A prompted NK cells to produce high levels of IL-5 and IL-13.

Mice immunized with the HHV-6B gH/gL/gQ1/gQ2 glycoprotein complex that is essential for virus infection developed protective immunity against infection with HHV-6B.

#### 4.2 Mouse model for pathogenesis and immunity (abstract 13-4)

Genome sequencing and phylogenetic analysis reveal that murine roseolovirus (MRV) is closely related to HHV-6A and -6B and HHV-7.
In newborn mice (but not in adults), infection with MRV results in CD4+ T cell depletion and in disruption of thymic structure. MRV was shown to trigger apoptosis in developing thymocytes following infection. CD8+ T cells that infiltrate the infected thymus were shown to contribute to the restoration of CD4+ T cell populations and the normal thymic architecture; however, CD4+ recovery mechanisms still remain elusive.

5 | GRAFT VERSUS HOST DISEASE, DIHS/DRESS

5.1 | HHV-6B and graft versus host disease (abstracts 5-1, 5-2)

Acute graft versus host disease (aGVHD) is a leading cause of morbidity and mortality following allogeneic hematopoietic cell transplantation (HCT). Reactivation of HHV-6B is detected in plasma and/or serum in ∼40% of post-CT patients at a median of 20 days after HCT. A metaanalysis presented at the conference showed a statistically significant temporal association between the appearance of HHV-6B viremia and subsequent aGVHD. Such associations are consistent with, but do not prove, a causal role for HHV-6B in aGVHD. The viremia could simply be an epiphenomenon.

Several studies that performed qualitative HHV-6B DNA PCR testing of diseased tissues in patients with aGVHD found the virus in diseased tissue more often than in similar healthy tissue, suggesting a causal role. However, the methods used to identify HHV-6 generally have not been able to distinguish between latent and lytic infection—an important limitation in studying a ubiquitous virus capable of lifelong latent infection. Advanced molecular techniques that allow for quantitative detection of viral nucleic acids in diseased tissue are required to demonstrate a causal role of HHV-6A and -6B in GVHD.

5.2 | Drug-induced hypersensitivity syndrome (DIHS)/drug reaction with eosinophilia and systemic symptoms (DRESS) (abstract 5-3)

DIHS/DRESS is a life-threatening, multi-organ system reaction induced by various drugs, predominantly anticonvulsants. As with aGVHD, many studies have found an association between DIHS/DRESS and HHV-6B viremia. Reactivation of several herpesviruses, including HHV-6B, is found in the great majority of patients with this illness, typically occurring 2-3 weeks after the onset. During the acute stage of the illness, populations of regulatory T cells (Tregs) are transiently observed, followed by a rise in Th17 cells. As with aGVHD, the question is whether the reactivation of HHV-6B is related to the pathology of DIHS/DRESS or is an epiphenomenon.

A small number of cases of DIHS/DRESS with organ failure and death have been studied, and HHV-6B has been found in the diseased organs. This observation is consistent with, but does not prove, a causal role for the virus in the more serious forms of DIHS/DRESS. Since the steroids that are often given to treat DIHS/DRESS could reactivate HHV-6B and other herpesviruses, several participants suggested treating DIHS/DRESS patients with antivirals in combination with steroids. This combination therapy should be validated in proper clinical trials.

6 | TRANSPLANTATION

6.1 | Viral reactivation and the immune response (abstracts 6-1, 6-2, 6-3, 6-4, 6-5)

Along with human cytomegalovirus (CMV), HHV-6B causes opportunistic infection following HCT. Reactivation typically is most evident in the first 2-6 weeks after transplantation and is associated with various illnesses and increased mortality. While a causal role for HHV-6B is generally accepted for post-HCT encephalitis, a causal role in other transplantation-related illnesses is not established.

Prior reports have suggested that HHV-6B reactivation post-HCT may be associated both with CD4+ depletion as well as delayed CD4+ immune reconstitution, and that the rate and magnitude of reconstitution is linked to various clinical outcomes. In particular, early CD4+ T-cell reconstitution has been associated with increased survival. HHV-6B infects CD4+ T-cells and causes selective apoptosis of these cells in vitro and in vivo. Also, HHV-6 infection of human thymocyte tissue results in severe and progressive thymocyte depletion.

Investigators provided an additional information on a recently reported retrospective study of 273 consecutive pediatric patients receiving HSCT, demonstrating that HHV-6 reactivation was less likely to occur in subjects with higher CD4+ T cell counts. They reanalyzed their data to determine if the HHV-6 reactivation occurred before or followed the poor CD4+ T cell immune response. Using univariate "time to event" models, they found that reactivation of HHV-6 had impaired reconstitution of CD4+ T cells at 200 days post-HSCT. HHV-6 reactivation also resulted in early and late poor CD8+ T cell recovery, but did not affect the reconstitution of B cells or NK cells. They also reported that 29 subjects with reactivation who were treated with ganciclovir or foscarnet in a non-randomized fashion (all for other viral infections) were more likely to have reconstitution of CD4+ cells than those with HHV-6B reactivation who were not treated. This was subsequently confirmed with multivariate analysis.

6.2 | Post-HCT encephalitis, pneumonitis, and hepatitis (abstracts 6-6, 6-7, 6-8, 6-9)

Japanese investigators reported a retrospective multicenter observational study of 6,593 HCT patients age 16 or older, of whom 2.1% developed HHV-6-related encephalitis, the great majority within 3-5 weeks post-HCT. Multivariate analysis revealed that male sex, cord blood donor cells, HLA-mismatched donors, and aGVHD prophylaxis by calcineurin inhibitors were significant risk factors for HHV-6-related encephalitis. In this uncontrolled observational study, renally adjusted full dose ganciclovir or foscarnet appeared to be superior to lower dose regimens for the treatment of encephalitis.
Although HHV-6B sometimes is detected in the lower respiratory tract post-HCT, and although pneumonitis of uncertain etiology occurs post-HCT, the role of the virus in causing pneumonitis has been unclear. Investigators tested bronchoalveolar lavage (BAL) samples obtained in the first 100 days post-HCT in 553 patients, and detected the virus in 27.8% of patients. In patients not on antivirals, plasma viremia was detected in 33.3% of patients with HHV-6-positive BAL specimens versus only 3.1% of patients with HHV-6-negative BAL specimens. Multivariate analysis demonstrated that patients with HHV-6-positive BAL specimens had a significantly increased risk of death (HR = 1.47).

Investigators reported a study of 101 children, median age 3.1 years, undergoing liver transplantation. About one third developed primary HHV-6 infection (initial seronegativity followed by plasma viremia), with associated fever and/or hepatitis. PCR testing of allograft biopsies revealed HHV-6 in most specimens along with signs of moderate rejection, lobulitis, and central venulitis.

7 | NON-CENTRAL NERVOUS SYSTEM DISEASE

7.1 | Roseola infantum/exanthem subitum (abstract 9-2)

Primary infection with HHV-6B causes roseola infantum (exanthem subitum) in many young children, and typically occurs in the first two years of life. Prompted by the observation of Japanese pediatricians that primary infection and roseola were occurring at older ages in the 21st century, Japanese investigators conducted a seroepidemiologic study of 491 children age 5 years or younger who visited doctors’ offices or emergency rooms with high fevers. Primary infection with HHV-6B was documented in 12% of the children, at a median age of 15 months. Older children (age 3-5) who developed primary infection were less likely to develop roseola than younger children (less than age 3) with primary infection, and also less likely to have leucocytosis and lymphocytosis. Also, in comparison to seroepidemiologic studies conducted in Japan the late 20th century, children experienced primary infection with HHV-6B at an older age.

7.2 | Cardiomyopathy (abstract 9-3)

Recent studies have suggested that HHV-6A and -6B (and icHHV-6) might be a cause of myocarditis and dilated cardiomyopathy, and other studies have reported that HHV-6A and -6B infection can induce functional and structural changes in mitochondria. Following up on these reports, investigators performed endomyocardial biopsies on a large number of patients with these heart muscle diseases. Patients with HHV-6A and -6B DNA in myocardial tissue were more likely to have a particular mitochondrial haplogroup (HV), suggesting that this haplogroup may be a risk factor for certain myocardial diseases following HHV-6A and -6B infection, and that the impairment of myocardial function seen in these diseases may reflect an impairment of mitochondrial energy production within cardiomyocytes.

7.3 | Salivary gland tumors (abstract 9-4)

Biopsies of 23 salivary gland tumors (20 malignant, 3 benign) and 7 normal salivary glands were examined for HHV-6A and -6B DNA (by species-specific PCR) and proteins (by immunohistochemistry using multiple antibodies). All 30 specimens (with or without tumors) revealed HHV-6A and -6B DNA. Most were positive for both HHV-6A and -6B, whereas, fewer were positive for HHV-6B only. Viral loads were much higher for HHV-6B than for HHV-6A. On the other hand, non-tumorous tissue was positive only for HHV-6B DNA whereas tumors were positive for both HHV-6A and -6B. In 10 of the 23 tumors, the tumor cells were uniformly positive for HHV-6 proteins, as was adjacent normal salivary gland tissue. HHV-6 proteins were also present in scattered areas of the normal salivary gland specimens. The investigators conclude that HHV-6A and -6B frequently infect salivary gland tissue, and that the question of whether they play a pathogenic role in the development of salivary gland tumors deserves additional study.

7.4 | Hashimoto’s thyroiditis (abstract 9-5)

Prior studies from Italy have frequently identified HHV-6 DNA and proteins in the thyroid glands of patients with Hashimoto’s thyroiditis (HT). An Iranian team pursued these reports in 151 patients with HT, 59 with other types of thyroid disease, and 30 healthy subjects without evidence of thyroid disease. They found HHV-6 viremia in 38% of patients with HT, 9% of patients with other thyroid diseases, and in none of the patients without thyroid diseases. People with HHV-6 viremia typically had higher levels of antibody against HHV-6.

7.5 | Primary infertility (abstract 9-7)

Infection of the endometrium with HHV-6A is strikingly more frequent in women with primary infertility than in fertile women or in women with secondary infertility. Investigators pursued biological risk factors that might influence the ability of HHV-6A to infect the endometrium, and risk factors that affect the pathologic endometrial responses to infection that may cause primary infertility. The investigators reported that particular single-nucleotide polymorphisms (SNPs) of the P2 × 7 receptor, an ATP-gated ion channel involved in the inflammatory response to infection, may be an important risk factor. HHV-6A infection was found only in women with this particular genotype. This result, if confirmed by others, indicates that the P2 × 7 variants could serve as a predictive biomarker for primary infertility.

8 | CENTRAL NERVOUS SYSTEM DISEASE

8.1 | Multiple sclerosis (abstracts 10-1, 10-4, 13-1, 13-3)

Multiple previous studies have suggested that HHV-6 infection may be one possible viral trigger and perpetuators of multiple sclerosis (MS). In what is likely the largest study of its type, investigators measured IgG...
serum antibodies against multiple HHV-6A and -6B antigens in two groups of patients and matched controls: 8744 patients with established MS and 7214 controls; and 480 pre-symptomatic patients (serum collected before the onset of relapsing-remitting MS) and 480 controls. Levels of anti-E1B IgG and anti-p100 IgG were increased in the patients with established MS ($P < 10^{-4}$ for both). Levels of anti-E1A were increased in patients with pre-symptomatic MS ($P < 10^{-5}$). These results are consistent with, but do not prove, a causal role for both HHV-6A and -6B in MS. Results for antibodies to other human herpesvirus antigens, particularly EBV antigens, were not reported, although sero-epidemiological evidence has identified EBV as a possible viral trigger for MS.

MS is a disease characterized by plaques of demyelination, prompting many investigators to seek viral triggers of demyelination. Theoretically, viral infection could also contribute to MS in another way: the brain and spinal cord have the ability to respond to demyelination with remyelination. In the brain, oligodendrocyte precursor cells (OPCs) migrate to areas of demyelination, differentiate into oligodendrocytes and proceed to remyelinate the naked neurons. Investigators reported that when HHV-6A U94, a latency-associated protein, is transduced with a lentiviral vector into human OPCs, the cells are much less likely to migrate into areas of demyelination. In addition, expression of genes known to be important in the migration of OPCs was down-regulated. This report supports the hypothesis that MS may result both from increased demyelination and from a failure of remyelination, and that HHV-6 may play a role in impaired remyelination. The relevance of this observation for human disease remains to be defined.

In transgenic mice that harbor human CD46, the receptor of HHV-6A, HHV-6A was shown to infect neurons and glial cells in the periventricular areas. These areas typically harbor plaques of demyelination in MS patients.

In a primate that naturally expresses the CD46 receptor—the common marmoset, Callithrix jacchus—intravenous inoculation with HHV-6A (but not HHV-6B) led to neurologic symptoms. Infected animals then were challenged with the antigens that produce experimental allergic encephalomyelitis (EAE)—a demyelinating condition considered an animal model for MS. HHV-6A infected animals exhibited earlier and more aggressive EAE than uninfected animals, and died sooner.

8.2 | Bipolar disorder and major depression (abstracts 10-3, 13-1)

Investigators studied post-mortem brains from 164 people with bipolar disorder (BPD), major depression (MD), schizophrenia (SCZ) or matched individuals with none of these diseases. They measured HHV-6A and -6B nucleic acids and proteins in the cerebellum, and found that the combination of nucleic acids and protein for both viruses was present significantly more often in patients with BPD and MD than in SCZ or controls. Infection appeared to be localized primarily to Purkinje cells. Gene expression analyses of cerebellar tissue found high expression of genes known to be involved in responding to viral infection and genes important in the function of toll-like receptors—key players in the innate immune response to infection.

This provocative result in humans was made more plausible by a study in transgenic mice expressing human CD46. The transgenic mice could be readily infected with HHV-6A and viral DNA persisted in the brain for the life of the mice (up to 15 months), while wild-type mice could not be infected with the virus. Upon infection of CD46 mice, HHV-6A was found in neurons and glial cells in the Raphe nuclei of the serotonergic pathway. Studies of the cerebellum had not been completed at the time of the conference. Intriguingly, CD46 mice infected with HHV-6A showed abnormal results in the tail suspension test, an accepted measure of anxiety and depression. In addition, infected mice were less active in the open-field test (a surrogate marker for depression) and stayed in the periphery of the open field (a surrogate marker for anxiety) compared to uninfected mice.

Investigators took transgenic mice expressing the human CD46 receptor and generated a transgenic line that also lacked toll-like receptor 9 (TLR9). In animals that expressed TLR9, infection with HHV-6A resulted in a greatly increased production of various cytokines and chemokines. In contrast, this inflammatory response was aborted in animals lacking TLR9. Animals with TLR9 intact demonstrated the same abnormal response on the tail suspension test as reported by the other team working with transgenic mice expressing CD46. However, this abnormal response was absent in mice lacking TLR9, suggesting that the inflammatory molecules and/or inflammation could cause the abnormal test results. This is of interest due to the growing evidence in humans that the chemistry of inflammation may play an important role in depression and anxiety.

9 | TREATMENT

9.1 | Prophylaxis for post-HCT encephalitis (abstract 7-1)

A multi-center open-label, single-arm trial of foscarnet was administered to 65 recipients of cord blood transplants from day 7 through day 21 post-transplant (82% completing the full course), and the results compared to historical controls. While the rate of HHV-6 viremia (systemic reactivation) was lower than in historical controls, the rate of encephalitis was not. All of the patients that developed encephalitis experienced “cytokine storm” (pre-engraftment immune reaction or aGVHD). At the same time, the investigators reported poor CNS penetration of foscarnet at the dose given (90 mg/kg per day, IV, in patients with normal renal function). They also reported that raising the dose of foscarnet in those who developed encephalitis appeared successful in treating the illness—a provisional conclusion, given that this was not a randomized trial.

9.2 | Adoptive immunotherapy (abstract 7-2)

One team reported the results of using adoptive transfer of virus-specific T (VST) cells to prevent and to treat viral reactivation in post-transplant patients. The technique involves obtaining blood from
the patient, identifying and expanding VST cells ex vivo, and then reinfusing the expanded cell population. The 10-day procedure produces T cell lines that target common opportunistic viruses: HHV-6, Epstein-Barr virus (EBV), CMV, adenovirus, and BK virus. In a small uncontrolled study that included 11 patients with reactivated HHV-6 infection, the investigators reported that the treatment appeared safe (induced minimal toxicity and did not trigger aGVHD) and that the VST cells crossed the blood-brain barrier. There was prompt resolution of both viral reactivation and associated illness symptoms, even in selected patients who had previously failed antiviral therapies. Proof of efficacy would require larger, randomized trials.

10 | FUTURE DIRECTIONS AND CHALLENGES

10.1 | Advances

Valuable new information was presented at the Conference about HHV-6A and -6B: about cell-viral interactions, the mechanisms by which the viruses integrate into host chromosomes, the immune response to infection, and mechanisms that influence the decision between latent and lytic HHV-6 infection. Valuable new information also was presented with regard to the possible pathogenic role of these viruses in various important human illnesses—in particular, post-HCT encephalitis and pneumonitis as well as aGVHD, DIHS/DRESS, Hashimoto’s thyroiditis, primary infertility, myocarditis and dilated cardiomyopathy, salivary gland tumors, multiple sclerosis, and mood disorders.

10.2 | Challenges

At the same time, no new disease associations have been proven since the previous (9th) International Conference. Indeed, it remains challenging to firmly establish a causal relationship between HHV-6A and -6B and any particular disease. This is because approximately 95% of the human race has a lifelong infection with the virus that is typically established in the first years of life. Establishing a causal role for the virus in disease will require several types of evidence: (i) HHV-6A and 6B nucleic acid, antigens, and viral gene transcription present with higher frequency in diseased tissue than in healthy tissue from same organ or other unaffected organs; (ii) An immune response to HHV-6A and -6B (cellular and/or humoral) in diseased tissue and/or blood; (iii) Viral nucleic acid levels in blood that are higher during disease flares; (iv) A virological and clinical response to antiviral or immunotherapy in a controlled setting.

Overall, it was great to see the steady progress that has been made since the 9th International Conference in 2015. While some questions can be addressed by individual labs and investigators, others will require multi-investigator collaborations. The 10th International Conference in Berlin demonstrated great examples of both approaches and defined a research agenda. This will hopefully inspire more high quality research to address the remaining questions of HHV-6 biology, immunology, disease associations, and management.

ACKNOWLEDGMENTS

We are indebted to Kristin Loomis and Dharam V. Ablashi, whose vision and leadership have greatly accelerated progress in studying the biology of human herpesvirus-6A and -6B and human herpesvirus-7 and their roles in human disease, through the establishment and many activities of the HHV-6 Foundation. We also are indebted to sponsors of the conference: Freie Universität, Berlin, Germany; National Institute of Allergy and Infectious Diseases, NIH; Clinigen; Biken; Ernst Reuter Foundation. Research reported in this publication was supported by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health under Award Number R13AI131614. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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SUPPORTING INFORMATION

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How to cite this article: Komaroff AL, Boeckh M, Eliason E, Phan T, Kaufer BB. Summary of the 10th International Conference on Human Herpesviruses-6 and -7 (HHV-6A, -6B, and HHV-7). J Med Virol. 2017;1–6. https://doi.org/10.1002/jmv.25004