

Roseoloviruses: unmet needs and research priorities

Perspective

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The human roseoloviruses, human herpesviruses 6A (HHV-6A), HHV-6B, and HHV-7, are highly prevalent viruses that typically cause fever/rash illnesses such as roseola during early life primary infections. They also cause significant neurologic disease and complications following stem cell and solid organ transplantation, and have suggestive but less certain etiologic associations with other neurologic diseases and immunologic disorders. The US National Institute of Allergy and Infectious Diseases recently sponsored a workshop (Roseoloviruses: Clinical Impact, Interventions, and Research Needs) to discuss disease associations, novel biology, and the many unmet research needs related to Roseoloviruses. This perspective is a distillation of the workshop's presentations and discussions, with a focus on the more general research priorities that emerged.

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The National Institute of Allergy and Infectious Diseases of the US National Institutes of Health recently sponsored a workshop entitled 'Roseoloviruses: Clinical Impact, Interventions, and Research Needs.' The meeting brought together over 50 clinical, translational, and basic science researchers, as well as scientific program officials to discuss the growing list of robust disease associations, novel biology, and unmet research needs related to Roseoloviruses.

The human Roseoloviruses are human herpesviruses (HHV) 6A, HHV-6B, and HHV-7 [1••]. These viruses are distinct, yet closely related members of the Roseolovirus genus of the Betaherpesvirus subfamily. They are

ubiquitous, infecting upwards of 95% of the human population; HHV-6B is best known as the major etiologic agent of roseola infantum and febrile illnesses in early childhood.

Roseoloviruses are also associated with more consequential pathologies, including neurological diseases and complications of both hematopoietic and solid organ transplantation. Although HHV-6 has long been listed as an Emerging Infectious Pathogen by the NIH, there remains a paucity of information about roseolovirus infections, and the full spectrum of diseases caused by roseoloviruses is not known. Limited understanding of their pathogenesis has slowed development of antiviral agents and therapeutic strategies. Unique features of roseolovirus biology, such as germline chromosomal integration of HHV-6 (ciHHV-6) in 1% of the human population have complicated the development of diagnostics and raise important biological questions.

To address these gaps, the workshop was convened to summarize the known health and societal impacts of roseolovirus infections, to identify critical barriers to the development of novel antiviral therapeutics and diagnostics, and to define high priority research questions. Articles by the meeting's speakers and their colleagues in this special issue of *Current Opinions in Virology* provide in depth summaries of the state of the art, and elaborate on research priorities for topics covered at the meeting (Table 1). This perspective is a distillation of the workshop's presentations and lively discussions, with a focus on the more general research priorities that emerged (Table 2).

Expanding recognition of the significant clinical impacts of roseolovirus infections

Primary HHV-6B and HHV-7 infections cause *roseola infantum*, or sixth disease. In addition, the roseoloviruses are neuropathogenic in immunocompetent and immunocompromised hosts. Reactivation of HHV-6B is a frequent complication of hematopoietic stem cell (HCT) transplantation, and the syndrome of post-transplant acute limbic encephalitis (PALE) is a recognized complication of HHV-6B reactivation in the early post-transplant period. This, plus the finding that 30% of febrile status epilepticus events in children are concurrent with periods of active infection with HHV-6B, adds to the previously noted connection between primary HHV-6B infection in children and febrile seizures.

Other diseases, including encephalitis in immunocompetent hosts, acute graft versus host disease, fever and rash

Table 1**Roseolovirus workshop: speakers and topics^a.**

Roseoloviruses: time for action (Robert C. Gallo, Institute for Human Virology)
 Roseolovirus impacts and needs: a community perspective (Kristin Loomis, Human Herpesvirus 6 Foundation)
 Clinical impact of primary infections with roseoloviruses (Mary Caserta, University of Rochester) [2]
 Roseoloviruses in immune compromised patients: impacts and prospects for clinical trials (Danielle Zerr, University of Washington) [3]
 Neurologic complications of roseoloviruses in immune competent children (Leon Epstein, Northwestern University) [2]
 The path to therapeutics for roseolovirus infections (Richard J. Whitley, University of Alabama at Birmingham) [4]
 Diagnosis of roseolovirus infections: what we know we don't know (Keith Jerome, University of Washington) [5]
 Roseoloviruses: a treasure trove of immune modulators (Amy Hudson, Medical College of Wisconsin) [6]
 Chromosomally integrated HHV-6: impacts on virus, cell, and organismal biology (Louis Flamand, Université Laval) [7]
 Animal Models (Paolo Lusso, National Institute of Allergy and Infectious Diseases) [8]
 Roseomics: a blank slate (Eain Murphy, Cleveland Clinic) [9]

^a References are provided for review articles prepared by the speakers and their colleagues for inclusion in this issue of *Current Opinions in Virology*. The special issue contains additional related articles [10–12].

following HCT, myelosuppression following HCT, hepatitis, allograft dysfunction, and pneumonitis have been associated with HHV-6, but these links remain tenuous. Their confirmation has been complicated by the ubiquitous nature of Roseolovirus infections, which are characterized by lifelong latency or persistence at several body sites. A further complication is that approximately 1% of the population harbors ciHHV-6.

An important research priority highlighted at the meeting is the development of rigorous criteria for identifying end-organ disease caused by primary or reactivated roseolovirus infection. Detection of viral DNA in blood or body fluids is informative, but moving beyond simple associations to proof of causality will require much more. Two approaches were suggested: (1) use of a specific treatment for HHV-6B disease (e.g., an antiviral or immunotherapeutic) to link viral replication with pathology, and (2) in-depth molecular interrogation of tissues involved in end-organ disease to identify pathologic and molecular signatures of HHV-6 infection.

Given the recent recognition of ciHHV-6, case reports associating high loads of HHV-6A or HHV-6B with disease should be reconsidered. Studies are needed to elucidate the mechanisms and pathogenic effects of ciHHV-6 in normal and immunocompromised hosts. Such information will impact not only individuals with ciHHV-6, but is also needed to assess the effects of ciHHV-6 on organ transplants.

Need for improved diagnostics and therapeutics

Molecular methods, including digital PCR, can identify ciHHV-6 and distinguish it from other forms of HHV-6 infection. Strides made in understanding the pathogenesis of cytomegalovirus disease illustrate how standardized units of DNA detection would improve our understanding of roseolovirus pathogenesis. Standardized measurement of viral DNA levels are needed to define clinically-relevant viral loads and for meaningful cross-institutional comparisons of viral loads. Further development and standardization of DNA qPCR and reverse

Table 2**Major basic science needs and clinical research objectives.****Foundational research objectives**

Assign functions to unknown genes and examine molecular interactions with host cells.

Standardize clinical isolates and cell culture infection systems.

Generate roseolovirus bacterial artificial chromosomes for genetic manipulation of virus.

Develop a broad panel of monoclonal antibodies.

Apply modern 'omics' methods to understand roseolovirus genomic variation, gene expression, and effects on host cell gene expression and activity.

Define the molecular mechanisms and consequences of Roseolovirus chromosomal integration.

Develop animal models to understand roseolovirus pathogenesis and evaluate therapeutic approaches.

Clinical research objectives

Epidemiologic studies to understand the natural history and clinical significance of ciHHV-6.

Rigorously evaluate associations between end organ disease and roseolovirus infection.

Standardize reliable DNA qPCR and RNA RT-qPCR assays with clinically relevant thresholds.

Interrogate cells and tissues for active viral infection or biomarkers of host responses to viral infection.

Robust clinical trials or longitudinal studies to prove or disprove disease associations.

Must distinguish between HHV-6A and HHV-6B.

Must define latent versus active infection and account for ciHHV-6.

Antiviral drug or immune therapy should result in reduced viral burden.

transcriptase-quantitative PCR assays are needed to enable discrimination between active and latent infections. New diagnostic tools are also needed for rapid detection and diagnosis of primary infection. Technologies suitable for point-of-care testing have the potential to alleviate unnecessary testing and antibiotic misuse. Such tools are critical precursors for the development and evaluation of scientifically based management and treatment protocols.

Only small-scale prophylaxis studies in HCT recipients have been published to date, and no antiviral drug is specifically licensed to treat HHV-6B disease. Newer compounds undergoing evaluation for the treatment of cytomegalovirus infections might prove useful for treatment of roseolovirus infections. A controlled therapeutic trial is needed for PALE and to determine whether prevention or inhibition of HHV-6B reactivation improves outcomes following transplantation. Unfortunately, a vicious cycle is at play, as clinical trials are needed to prove causality between infection and disease, while at the same time well-established pathologic associations are needed to justify drug development and clinical trials. Breaking this 'log jam' was recognized as one of the greatest challenges to the field.

Major gaps in understanding roseolovirus molecular virology and pathogenesis

State-of-the-art technologies must be applied to better define the host-pathogen 'interactome.' In-depth genomic analyses of uncultured clinical strains of roseoloviruses will help to identify possible disease-specific pathogenesis determinants. A multi-center repository of viral and human specimens from longitudinal studies is needed to enable such studies. Proteomics and metabolomics can open the door to identification of unique viral functions that would inform pathogenesis and serve as targets for new therapeutics. A basic molecular infrastructure of genetic systems, libraries of recombinant viruses, cloned ORFs for screening, and monoclonal antibodies is needed to define mechanisms by which roseoloviruses modulate host biology (e.g., immune responses) at the cellular and organismal levels. Animal models that recapitulate human disease are being developed in mice and non-human primates.

Time to act

Rigorous proof of etiologic associations of these ubiquitous but neglected human pathogens will require coordinated investment in improved diagnostic methods, and development of safe and specific antivirals. Therapeutic approaches will need to be evaluated in well-designed,

controlled trials that include meaningful clinical and virologic endpoints. In addition, and as has been the case for other important pathogens, a solid understanding of basic roseolovirus biology is an essential critical underpinning for future work.

A roadmap has been drawn. It is time to move forward.

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References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

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