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Editorial overview: Roseoloviruses: Stopping to smell the roses — the Roseoloviruses have come of age as human pathogens

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Dr Laurie T Krug is an Assistant Professor at Stony Brook University. She began her research career as a graduate student in Dr Philip Pellett's laboratory studying the human herpesvirus 6B U94 gene and Roseolovirus origin-binding proteins. While a postdoctoral fellow with Drs Margaret Offermann and Samuel Speck at Emory University she studied the molecular biology, immunobiology, and pathogenesis of human herpesvirus 8/Kaposi's sarcoma-associated herpesvirus and murine gammaherpesvirus 68 (MHV68). Dr Krug's laboratory examines the role of virus and host determinants in gammaherpesvirus pathogenesis using the MHV68 mouse pathogen model system. Her three major areas of investigation are: virus-host interactions that influence latency and viral gene expression in B cells; the role of tegument proteins in signaling and replication processes; and innate and adaptive immune mechanisms of host control and the virus counter-defense. Dr Krug was a member of the organizing committee for the recent National Institutes of Health Workshop 'Roseoloviruses: Clinical Impact, Interventions, and Research Needs.'

Four human herpesviruses were discovered in a eight-year period between 1986 and 1994. This exciting era of virus discovery was driven in part by the search for HIV and HIV-related diseases coupled with the development of new molecular tools such as PCR, automated Sanger sequencing, and subtractive hybridization. Three of these viruses, human herpesvirus 6A (HHV-6A) and human herpesvirus 6B (HHV-6B), and human herpesvirus 7 (HHV-7), were initially cultured from peripheral blood mononuclear cells. All three were found to be T lymphotropic viruses that were most closely related to human cytomegalovirus (HCMV), placing them in the betaherpesvirus family. Given their tight biologic and genetic relationships and clear etiologic link to roseola infantum, these viruses are now designated *Roseoloviruses*. Human herpesvirus 8 (also known as Kaposi's sarcoma associated herpesvirus) was identified as a new member of the gammaherpesviruses, in the rhadinovirus genus. Given its clear link to HIV-related malignancies, HHV-8 research exploded.

So began the struggle of the roseoloviruses for recognition and funding in the competitive world of biomedical research. The rate of discovery of their pathogenic potential has lagged compared to HHV-8 but great progress has been made nonetheless. This special section on the *Roseoloviruses* is intended to update the scientific community on the clinical impact, molecular virology, pathogenesis, and technological advancements in the field. The collection of reviews is a tangible product of a recent National Institutes of Health Workshop that brought roseolovirus experts together to discuss the clinical and basic science priorities of the field, summarized in the Perspective piece by Caserta *et al.* Each of these reviews highlights recent findings that address important aspects of 'roseolobiology' and each provides direction for further pursuits to fill-in specific gaps in knowledge.

Roseolovirus cytopathic effect is striking. Anyone who has witnessed the ballooning, refractile cells upon infection will wonder at the power of these viruses to cause such fundamental change in target cells. Krug and Pellett present an overview of unique features of the roseoloviruses and explore the genetic content of these viruses, pointing out the genes common to betaherpesviruses and those unique to the roseoloviruses. There are dozens of viral genes with unknown functions that will certainly provide important insight into the molecular basis of infection and disease. These gene products, in addition to newly discovered miRNAs, are untapped resources to understand how these viruses hijack reservoirs in the host such as T cells and astrocytes. A forward-thinking review of 'omics' technologies by

Moorman and Murphy provides a tantalizing look at how systems-based approaches might be applied to rapidly bring the molecular biology of roseoloviruses in line with other human herpesviruses. They advocate for genomics analysis of clinical isolates to establish reference strains and identify disease-associated variants, genome-wide gene expression studies to validate and classify the kinetics of transcripts, and functional screens of tagged-ORF expression libraries and BAC-based recombinant ORF mutant libraries coupled with proteomics to quickly ascribe gene function and viral protein interactions.

The review by Frenkel *et al.* is a telling story of how the roseoloviruses push the cell cycle into the G2/M phase and remarkably harness the E2F transcription factor to regulate the expression of the HHV-6A U27 and U79 genes. The unfolding mechanisms of virus subversion of both innate and adaptive immune responses is told by Amy Hudson. The roseolovirus repertoire includes gene products that target cytokine signaling, T cell activation, and downregulate MHC class I antigen presentation. Defining the role of viral immune modulators and uncharacterized genes will require experimentation in the whole animal to be realized. Horvat *et al.* summarize how the CD46-trangenic and humanized mouse models and non-human primate models recapitulate different aspects of roseolovirus disease in humans.

One striking feature of HHV-6A and HHV-6B is their ability to integrate into the telomeres of the human chromosome, in some cases resulting in heritable transmission of the viruses. Approximately 1% of the population harbors germline integrated HHV-6A or HHV-6B; chromosomal integration is a steadfast aspect of HHV-6A and HHV-6B biology. The review by Kaufer and Flamand describes recent advances in cell culture systems that allow researchers to examine how HHV-6A or HHV-6B integrate and excise themselves from host chromosomes. A pressing issue for the integration of HHV-6A and HHV-6B is determining if this is a requisite part of the virus lifecycle, potentially representing a novel mechanism for latency. Clearly, the clinical consequences of an integrated herpesvirus, whether in a few somatic cells or integrated into every cell of a human, requires further investigation.

Roseola infantum (*Exanthema subitum*) is a hallmark childhood illness comprised of a high fever lasting 1–5 days in duration that may be followed by a maculopapular rash. Tesini *et al.* summarize a series of clinical studies indicating that serious complications, such as febrile seizures and febrile seizure epilepticus, can arise from primary infection with HHV-6B and HHV-7. Human cytomegalovirus has long been associated with transplant complications, in part due to reactivation upon immunosuppression. As described by Hill and Zerr, allogeneic hematopoietic stem cell transplant patients, and in particular cord blood stem cell recipients, are at higher risk of HHV-6B reactivation associated with limbic encephalitis and neurocognitive disorder. A balanced review of the current literature regarding the association of the neurotropic roseoloviruses with multiple sclerosis (MS) is presented by Leibovitch and Jacobsen. Evidence for both direct roles of the virus and virus-driven immune responses in MS pathology are discussed.

Diagnosis of primary roseolovirus infection and CNS-related complications arising from both primary infections and reactivation in immunosuppressed transplant patients would benefit from rapid diagnostics and less toxic antiviral drugs. Hill *et al.* introduce the use of digital PCR to distinguish single integrated viral genomes per cell in patients with chromosomal integration of HHV-6A or HHV-6B (ciHHV-6) from a high copy number of virus in a blood sample due to viral reactivation. This review also highlights the importance of using other molecular tools such as quantitative reverse-transcript PCR of mRNA to distinguish latent from active, lytic infections.

Clinicians need safe and effective therapies to control roseolovirus infection and limit viral pathogenesis. The efficacy of current nucleoside analogs and of drugs in the developmental pipeline is reviewed by Prichard and Whitley. The authors point out that there is little fiscal incentive for the pharmaceutical industry to dedicate research and development to the roseoloviruses without clear disease etiology. However, Koch's postulates are difficult to fulfill for ubiquitious viruses. In a frustrating case of 'Catch-22', clinical trials with roseolovirus-specific drug therapies are key to demonstrating that virus infection leads to the resolution of a suspected roseolovirus-associated disease. Immune therapy shows real promise in the treatment of reactivation-associated disease in transplant recipients. Becerra *et al.* define the predominant HHV-6A and HHV-6B epitopes that CD4+ T cells and CD8+ T cells recognize and explain how these T cells can be expanded in culture for autologous transfer and protection.

These last several years have produced a collection of new data, technologies, and ideas that generates important new questions about roseolovirus biology. Can we treat reactivation and nervous system disease with novel antivirals and immune therapy? Does an integrated virus place a patient at risk for disease? Is integration a part of the virus lifecycle? What are the functions of uncharacterized gene products during infection, and how do they impact pathogenesis? Can we confirm or discount roseolovirus causality or contributions to rare or complex diseases? We direct the reader to the focused reviews on the molecular and clinical aspects of HHV-6A, HHV-6B, and HHV-7 in this special section on the *Roseoloviruses*. It is time to stop and smell the roses.