Online summary:

- Herpesviruses are a ubiquitous, large, diverse family of double-stranded DNA enveloped viruses capable of infecting a wide range of hosts and causing a variety of diseases. Prototypical herpesviruses are herpes simplex virus (HSV) types 1 and 2, and Epstein-Barr Virus (EBV), which cause oral herpes, genital herpes, and mononucleosis, respectively.
- Herpesviruses use common mechanisms to bind to and enter target cells through a process of virus-induced membrane fusion. These conserved mechanisms are explored here using HSV and EBV as examples.
- Relative to other enveloped viruses, herpesviruses require a large number of glycoproteins in order to accomplish fusion. The conserved core set of glycoproteins required for entry are glycoprotein B (gB) and a heterodimer composed of glycoprotein H (gH) and glycoprotein L (gL), referred to as gH/gL. Additional required glycoproteins are the receptor-binding HSV glycoprotein D (gD) and EBV glycoprotein 42 (gp42). The structures for each glycoprotein required for virus entry as well as three of the cellular receptors that bind virus and/or trigger fusion are now known.
- Both EBV and HSV infect multiple cell types through engagement with different receptors. Although their primary receptor-binding proteins are different, HSV and EBV fusion with most cell types is triggered when their receptor binding proteins bind receptor and a resulting conformational change triggers the viral glycoproteins that drive fusion.
- Viral glycoproteins gH/gL and gB are conserved within the herpesvirus family. The crystal structure of gB revealed that it is a viral fusion protein, capable of inserting into target membranes and inducing fusion through conformational changes.

- The specific role of gH/gL in fusion has eluded researchers for years. Evidence suggested that it was an additional fusion protein, however the recently solved structures of gH/gL reveal, surprisingly, that it does not resemble any known fusion protein. A new model of herpesvirus fusion is emerging in which gH/gL acts as a regulator of gB through direct gH/gL-gB binding.
- Herpesvirus fusion is a remarkably complex process. Now that the structures of all major glycoproteins and receptors involved in herpesvirus fusion are known, they can be used for the rational design of novel attachment and fusion inhibitors against these ubiquitous human pathogens.