NIH Award from the National Institute of Allergy and Infectious Diseases

Principal investigator: Greg A. Smith, microbiology-immunology, Feinberg School of Medicine

- **Project:** Alpha-Herpesvirus Assembly, Egress and Viral Particle Heterogeneity
- **Start Date:** September 1, 2009
- **Total Award Amount:** $303,761

**How the results of this project will benefit society:**
Neuroinvasive herpesviruses are the causative agents of a number of severe diseases including shingles, encephalitis, neonatal infections and herpes keratitis (the leading cause of infectious blindness in America). This proposal focuses on understanding the molecular mechanisms that underlie the assembly and egress of herpesvirus particles, with the long-term goal of identifying new targets for the intervention of disease progression.

**The problem the project is trying to solve:**
The neuroinvasive herpesviruses are a highly-prevalent group of the alpha-herpesvirus subfamily that includes the human pathogens: herpes simplex virus types 1 and 2 (HSV–1, HSV-2), and varicella zoster virus (VZV). An additional member of this group is a virus of veterinary significance, pseudorabies virus (PRV), which historically has provided models for studying viral pathogenesis. Despite the availability of the antiviral compound acyclovir, several severe forms of disease caused by these viruses remain prevalent in this country and worldwide. Infections associated with high rates of morbidity or mortality include encephalitis, keratitis, shingles and disseminated infections in newborns. Novel strategies to interfere with the assembly and egress of these viruses could prove valuable to treatment of infections, yet much of the herpesvirus infectious cycle remains undefined.

**How this project will work:**
In this application we leverage our expertise in infectious clone mutagenesis and single viral particle fluorescence imaging methods to dissect viral structural composition in living-cells and extracellularly, and to address the molecular pathways guiding viral assembly and egress. New evidence is provided indicating that the very large herpesvirus tegument protein, VP1/2, is a key effector of viral assembly. This proposal is based on the hypothesis that herpesvirus assembly and egress are coupled processes that occur through a series of sequential steps both in the nucleus and cytoplasm of infected cells, and that each of these steps are effected in part by the VP1/2 protein. Our goal is to refine our understanding of these steps at the level of the protein interactions that contribute to the dynamics of viral egress. This proposal includes comparative studies of model viruses from the two neuroinvasive herpesviruses groups, the simplexviruses (represented by HSV-1) and the varicelloviruses (represented by PRV), to develop a comprehensive analysis of the properties of these viruses.

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