**Medical Education and Research Grant Outcome Report**

**Name:**  Cellular and Viral Determinants of Human Cytomegalovirus Lytic and Latent Replication Cycles

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**Department:** Oncology  
**Program:** New Investigator Program  
**Grant Duration:** 02-01-06 to 08-31-08 (30 months)  
**Expenditures:** $100,000 (100% expended)  
**Use of Funds (Taxonomy):** Basic research  
**Research Keywords:** Cytomegalovirus, latency, gene expression, atherosclerosis, cancer

**Description:** Human cytomegalovirus (HCMV) is a widespread pathogen that infects the majority of the population. It causes birth defects, promotes disease in immunocompromised patients, and likely contributes to atherosclerosis and certain cancers. HCMV infections are life-long because the virus can enter and exit a dormant state called latency, in which it avoids detection by the host's immune system. Cellular determinants that control the latency of HCMV are unknown, and there are no antiviral treatments for latently infected cells. This contributes to our inability to cure certain viral infections such as HCMV and human immunodeficiency virus (HIV).

The investigators set out to: (1) determine if a certain cellular protein, Daxx, is responsible for latent viral infections, (2) identify any cellular proteins that control the localization of the pp71 protein inside cells, and (3) identify any viral protein that may control pp71 localization.

**Results:** The results revealed that, in order to establish latency, HCMV appears to use one of the cell's antiviral defenses that evolved to inhibit productive (lytic) infection. The results also allowed the investigators to propose a model in which certain other viruses may use cellular defenses as a way to establish latent infections—thus allowing the virus to avoid immune detection while co-existing for the life of the host.

Specifically, the findings revealed that the Daxx protein silences HCMV gene expression when quiescent infections that resemble latency are established. Daxx is also involved in true latent infections in the more physiologically relevant CD34+ stem cells. In addition to this cellular protein, the investigators concluded that a viral protein also contributes to the viral gene silencing observed when latent infections are established. Other work determined that cellular proteins, and not viral proteins, are likely to control the sub-cellular localizations of pp71.

The findings offer an innovative approach that changes the way scientists think about antiviral defenses and latent infections. The findings also identified a new cellular target (Daxx) for a potential antiviral treatment. Because cellular genes mutate much more slowly than do viral genes, resistance is much less likely to develop against drugs that affect cellular proteins. As cellular targets for antiviral treatment attract more attention, these results point to a specific type of cellular proteins that may be key treatment targets.

**Met Objectives:** Project completed

**Timeline for Application of Results:** 5-7 years

**New Partnerships or Collaborations:** None

**Matched Dollars (cash or in-kind):** $0

**Dissemination:**
- Published article: *Journal of Virology*
- Presentations/posters at: International Herpesvirus Workshop; American Society for Virology Conference; Gordon Research Conference; American Society for Microbiology Conference

**Additional Funding:** National Institutes of Health—5-year funding at $225,000 per year.