

02-1133

David M. Lukac

**“Synergy of KSHV ORF57 with the lytic switch protein. “**

**[An investigation of the cooperation of two proteins from Human herpesvirus-8 in promoting spread of the virus within the infected host and stimulating growth of AIDS and non-AIDS associated malignancies.]**

This project will help to answer questions concerning infection by a recently-discovered human virus and its contribution to AIDS-associated and non-AIDS-associated cancers. This virus, called Kaposi's Sarcoma-Associated Herpesvirus, or KSHV, infects B cells of the immune system, where it establishes latency, or undetectable residence. However, when the cells in which the virus resides become properly stimulated, or when the immune system of the host becomes weakened (as in AIDS), the virus re-emerges to reproduce itself and spread to new sites of infection. Such re-emergence, or reactivation, is associated with increased risk of two different malignancies: primary effusion lymphoma, a B-cell cancer, and Kaposi's Sarcoma, a cancer of the lining of lymph vessels. Thus, to fully understand how KSHV contributes to human cancers, we would like to study cellular and molecular processes that control reactivation of the virus. We have identified the key viral protein, called OR.F50, or Rta ("Replication and transcriptional Activator"), which controls the reactivation of the virus from latency in B cells. We have also determined that a second viral protein, called OR.F57/Mta, dramatically enhances OR.F50's molecular function. We would like to investigate the mechanism by which OR.F57/Mta synergizes with OR.F50/Rta in order to reveal key points of molecular regulation of OR.F50's function. Such knowledge will suggest ways in which to reduce or eliminate the risk of such a viral infection leading to cancer by inhibiting the function of the viral molecules that are responsible for, directing the reactivation, or directly counter-acting the cellular proteins that contribute to reactivation of the virus.

In general, these experiments will also reveal key cellular molecules that control normal cell growth and immune function, but are vulnerable to disturbances, such as viral infection, which can inhibit the normal duties of these molecules and lead to cancer. Since primary effusion lymphoma and Kaposi's sarcoma are very unique cancers, these experiments will not only help reveal unique molecular contributions to human cancers, but also will help reveal unique molecular targets and strategies for cancer detection and prevention. Since these cancers are more common in AIDS patients than in the general population, this proposal has special relevance for citizens of New Jersey, considering the proximity to New York City, one of the original epicenters of the AIDS epidemic, and considering that New Jersey was one of the only states which saw an increase in reporting of new AIDS cases in the year 2000.