

## Bankhead-Coley Cancer Research Program

***Harrington, William***

*Department of Medicine  
University of Miami*

*2007 Program  
Specialized Programs of Research Excellence  
(3-year project)*

**Project Title:** Pathogenesis and Therapy of Viral Lymphomas

**Project Summary:** Viruses are considered the second most important cause of malignant disease in humans and are highly associated with aggressive lymphomas including Adult T-cell Leukemia/Lymphoma (ATLL) (HTLV-I), non-Hodgkin's (NHL), and Hodgkin lymphoma (EBV). South Florida is endemic for these pathogens due to its close proximity to the Caribbean and large population of chronically immunocompromised patients including organ transplant recipients and AIDS cases. The incidence of NHL is increased nearly 200-fold in HIV-positive patients and our institution cares for the largest number of viral (HIV)-associated lymphomas in the country. As a major viral oncology center, our institution has unique strengths in the area of immunodeficiency related tumors, particularly lymphoma. This is reflected both in our investigator's publication records and NIH grants, as well as our activity in the NCI-sponsored AIDS malignancy (AMC) clinical trials consortium (we have accrued the most lymphoma patients of any institution). UM/JMH is the ideal site for combining both clinical and basic research from which to develop a multi-investigator program focused on viral lymphomas. Project 1 focuses on the mechanisms of antiviral resistance in ATLL. These tumors, which are quite common in South Florida and very common in the Caribbean, are aggressive and unresponsive to conventional chemotherapy. We have found that the transcription factor IRF-4 and the NF-kappaB subunit c-Rel are associated with resistance to interferon (IFN-alpha) based therapy. We will study how these factors inhibit IFN within the context of a prospective clinical trial for ATLL and utilize a murine model of ATLL that recapitulates IRF-4+ ATLL to clarify these mechanisms. Project 2 will focus on the development of novel prognostic models for HIV-associated large cell lymphoma, the second most common form of cancer in these patients. Dr. Lossos has developed methods that will allow analysis of RNA from paraffin embedded specimens from our own extensive tumor library at UM/JMH as well as those linked to prospective clinical trials. The development of applicable novel molecular markers will allow for the design of targeted and less toxic approaches for immune-compromised patients with high grade lymphoma. Project 3 will focus on determining the mechanisms whereby oncogenic viruses such as EBV escape innate immune surveillance. Recently Dr. Barber's laboratory has shown that vesicular stomatitis virus, VSV, a relatively non-pathogenic, RNA virus, can selectively kill cancer cells, including lymphoma, but not normal cells. This occurs because cancer cells exhibit a flawed anti-viral system, which is essential for preventing virus replication. The ability to genetically manipulate this simple virus offers an ideal opportunity to develop a targeted therapy for B-cell lymphomas. Dr. Rosenblatt and co-workers are developing a fusion protein that combines a clinically efficacious anti-B cell CD-20 with a ligand that has been shown to recruit cytotoxic NK cells in a breast cancer model. This is a potentially exciting way to enhance an already targeted form of lymphoma therapy and will be the focus of a developmental project. These activities will also serve as unique platforms for training of young investigators in both clinical and basic aspects of AIDS oncology. This proposal

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is also designed to promote collaborative efforts in anticipation of submission of an NCI SPORE application.