

Bankhead-Coley Cancer Research Program

Lossos, Izidore

*Department of Medicine
University of Miami*

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Project Title: Prognostic Models in Diffuse Large B-Cell Lymphoma

Project Summary: Diffuse large B-cell lymphoma (DLBCL), a most common type of non-Hodgkin's lymphoma, is characterized by marked biological and clinical heterogeneity. In the era of previous standard therapy of this disease—cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP), it was demonstrated that survival of DLBCL patients can be predicted by measurement of expression of a limited number of genes. However, the standard treatment has evolved to include the rituximab, an anti-CD20 antibody with CHOP (R-CHOP). Initial studies suggest that addition of rituximab changes the predictive power of specific molecular biomarkers, and it is possible that new biomarkers associated with the anti-tumor effects of rituximab may become prognostically significant. Therefore, there is an urgent need to establish reliable biomarker-based prognostic models for DLBCL patients treated with the current standard regimen of R-CHOP, which will potentially change the way we practice medicine. In addition, all the previous models were based on RNA measurement in frozen specimens, which have limited availability, thus restricting applicability of the proposed prognostic models. Construction of prognostic models based on widely available paraffin-embedded tissue samples for analysis of gene expression would allow immediate and widespread applicability of these models in daily clinical practice. This project is based on a new methodology of RNA extraction from formalin-fixed, paraffin-embedded tissues (developed in the research team's laboratory), which allows reliable measurement of gene expression by either real-time PCR or oligo-microarrays. This methodology will be used to accomplish the goals of the proposal that include the following:

1. Identify a list of genes whose expression correlates with survival of DLBCL patients treated with R-CHOP by array-based gene expression profiling. This will allow future construction and validation of a paraffin-based real-time PCR gene expression prognostic model based on RNA derived from paraffin specimens.
2. Examine the survival predictive power of rituximab-receptor variants, which may be associated with the anti-tumor effects of rituximab in DLBCL patients treated with R-CHOP. These studies should define molecular prognostic models for the most common type of lymphoma that will be used in clinical practice and will add to the prognostic power of the current clinical prognostic indexes. Routine application of the prediction models will enable identification of patients at high risk for standard therapy failure and may form the basis for risk-adjusted therapies for DLBCL. Furthermore, identification of genes-proteins comprising the predictive models will point to distinct pathogenesis mechanisms of DLBCL subtypes and potentially lead to recognition of new molecular therapeutic targets. Further, establishment of a paraffin-based RNA prognostic model using the new methodology of RNA extraction could serve as a paradigm for other lymphomas and tumors.