

Bankhead-Coley Cancer Research Program

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Bridge (1-year project)*

Project Title: Negative Regulation of the MHC Class II Promoters

Project Summary: Cells develop into tumor cells because of mutations that occur in multiple genes. In the most common case, the mutations accumulate over many years until a potentially lethal cancer cell develops. One of the several classes of genes that are mutated in lethal cancer cells is termed "tumor suppressor genes." These genes encode proteins that regulate, and often inhibit, cell division, and when there are mutations in a member of this class of tumor suppressor genes, the cell can divide uncontrollably. In 1994, the grantee's group reported the discovery that one of these tumor suppressor genes, the retinoblastoma tumor suppressor gene (Rb), is required for the expression of a set of proteins that are recognized by T-cells, termed the major histocompatibility (MHC) class II proteins. Thus, this discovery linked a breakdown in the regulation of cell division with a breakdown in the immune functions that contribute to preventing the spread of cancer throughout the body. Without the proper expression of the MHC class II genes, T-cells cannot recognize the cancer and thus cannot participate in reducing the spread of cancer. The bridge funding will be used to further our understanding of why the MHC class II genes are not expressed in cells with a mutated Rb tumor suppressor gene, especially bladder carcinoma cells. For example, the research team has strong preliminary data, from somewhat artificial, experimental systems, indicating that a protein termed YY1 represses one of the MHC class II genes when the Rb protein is mutated. However, the team has not yet determined conclusively whether YY1 represses the MHC class II gene under more natural conditions. This determination will be made using the bridge funding, which will very likely support a more extensive application to the NIH that would be designed to determine the exact molecular mechanism of YY1-mediated repression of the MHC class II gene. This in turn will lead to proposals for therapeutic elimination of YY1 and re-expression of the MHC class II gene in patients' cancers, thus facilitating the eradication of the cancer by the patient's T-cells. Importantly, this research team has shown with previously published work that MHC class II expression does not occur in a wide variety of cancer cells that lack the Rb tumor suppressor protein, unless the Rb-protein has been replaced by experimental approaches. Thus, the bridge funding is expected to lead to the development of novel treatments for numerous different types of cancers that develop due to Rb-mutations, including lung, breast, and bladder cancers.