

Bankhead-Coley Cancer Research Program

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Project Title: Notch Signaling in Chemotherapy of Multiple Myeloma

Project Summary: Multiple myeloma (MM) is a hematologic malignancy that results from a proliferation of clonal plasma cells, which accumulate preferentially in the bone marrow. It ranks as the second most frequently occurring hematologic cancer in the United States after non-Hodgkin's lymphoma. Approximately 15,000 new patients are diagnosed each year, with 11,000 people dying each year from myeloma. Multiple myeloma is a treatable but rarely curable disease. Chemotherapy significantly improves prognosis. However, treatment still remains unsatisfactory with a median survival of 3-6 years and a 10-year survival of 3 percent. The most common clinical problem in treatment of multiple myeloma is the resistance of malignant cells to chemotherapy. Understanding the mechanisms of this resistance is critically important for the development of the most effective treatment of these patients. Recently it became increasingly clear that bone marrow environment and specifically bone marrow stroma play a major role in survival of multiple myeloma and its resistance to chemotherapy. The main question is how to utilize this information for the development of new therapeutics. This would be possible with the identification of the molecular mechanisms responsible for resistance of multiple myeloma cells to chemotherapy. In this case, targeted therapeutics could be used. The research team has recently discovered that receptor/transcriptional regulator Notch is one of the major factors responsible for protection of myeloma cells from drug-induced apoptosis. In preliminary experiments, the team has demonstrated that inhibition of Notch signaling with gamma-secretase inhibitors kills MM cells without affecting normal bone marrow cells and substantially enhances the effect of chemotherapy. Here, the team's intent is to investigate the mechanisms and clinical significance of these novel findings as well as potential approaches to use this new information in treatment of multiple myeloma. The overall goal of this proposal is to identify a new therapeutic strategy based on Notch signaling that will improve the effect of chemotherapy of MM. To achieve this goal we propose studies under the following two specific aims:

Hypothesis 1. MM up-regulate expression of Notch ligands on BMS that contribute to enhanced signaling of one particular member of Notch family – Notch-1, which results in protection of MM cells from chemotherapy.

Specific Aim 1. Study the role of different members of Notch family and Notch ligands in mechanisms of Notch-mediated protection of myeloma cells from drug-induced apoptosis.

Hypothesis 2. Inhibition of Notch signaling with gamma-secretase inhibitors causes direct cytotoxic effect on MM cells and/or makes them more sensitive to chemotherapy.

Specific Aim 2. Investigate the effect of inhibition of Notch signaling on myeloma cells' response to chemotherapy.