

Bankhead-Coley Cancer Research Program

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Bridge - New Investigator
(2-year project)*

Project Title: Role of Bim in Mediating CAM-DR in Hematopoietic Tumors

Project Summary: Most leukemia patients will initially respond to chemotherapy. However, the emergence of drug resistance continues to support the importance of identifying and targeting drug resistant mechanism(s) as a viable strategy for improving the efficacy of cancer chemotherapy. Traditionally, drug resistance mechanisms have been identified and functionally characterized in unicellular tumor models. However, unicellular models lack consideration of host-tumor cell interactions that may participate in the emergence of the drug resistant phenotype. The research team proposes that the initial selection pressure for tumor growth and survival is represented by host-tumor cell interactions and, furthermore, these same interactions may participate in modulating drug response. It is well accepted that initial chemotherapy of chronic myelogenous leukemia and acute myeloid leukemia results in rapid clearing of detectable disease in the peripheral blood. However, elimination of disease in the bone marrow is a more arduous task, suggesting that de-novo drug resistance of leukemia cells associated with the bone marrow microenvironment may contribute to Minimal Residual Disease (MRD) following chemotherapy. This team has reported numerous findings that adhesion of hematopoietic tumors via beta1 integrins confers a multi-drug resistant phenotype. More recently, their laboratory demonstrated that adherent leukemia cells have reduced levels of the pro-apoptotic BCL-2 family member Bim. Reducing the levels of pro-apoptotic molecules generally increases the ability of tumor cells to resist death following exposure to chemotherapy. Based on these findings, the team has hypothesized that adhesion of leukemia cells via beta1 integrins in the bone marrow microenvironment contribute to the failure of conventional chemotherapy to eliminate minimal residual disease and thereby increases the incidence of disease relapse. For this proposal both an in vitro and in vivo model will be used for investigating the best approach for circumventing drug resistance associated with adherent leukemia cells located in the bone marrow microenvironment. The goal of Specific Aim 1 will be to determine the causal role of Bim in mediating the drug resistant phenotype in adherent leukemia cells. In Specific Aim 2, they will utilize pharmacological inhibitors of beta1 integrin mediated signaling to test for increased Bim expression and drug sensitivity in the in vitro and in vivo model of the bone marrow microenvironment. Finally, in Specific Aim 3, the molecular pathway whereby Bim is degraded in adherent leukemia cells will be delineated. These studies will hopefully provide novel targets for increasing Bim levels in adherent cells. In summary, the team proposes that more complex models that consider the microenvironment are needed to evaluate and delineate mechanisms of resistance that contribute to the failure of conventional chemotherapy to eradicate minimal residual disease in leukemia patients. In this grant, two models will be utilized to determine pre-clinically whether disruption of beta1 integrin-mediated signaling will enhance the efficacy of chemotherapy in the bone marrow microenvironment.

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