

Bankhead-Coley Cancer Research Program

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Project Title: c-Met Mediated Ovarian Cancer Cell Motility

Project Summary: Ovarian cancer is the most lethal of the gynecologic cancers and is the fourth-leading cause of cancer death among women in the U.S. Approximately 22,200 women were diagnosed with ovarian cancer in 2005, along with approximately 16,210 deaths. Currently, 50 percent of women diagnosed with ovarian cancer die within five years; when diagnosed in advanced stages, the five-year survival rate is approximately 15 – 20 percent. The current standard of care for treating ovarian cancer is cytoreductive surgery followed by chemotherapy. However, chemotherapy drugs do not differentiate well between normal and tumor cells. Toxicities produced by chemotherapy cause severe damage to normal cells that can limit the dosage strength tolerated by the patient and degrade the patient's physiological condition. Thus, treatment regimens that can specifically target molecules involved in signaling pathways that are activated in cancer cells may alleviate the toxicity and are in great demand. In ovarian cancer, as in most other solid tumor, metastasis is a major cause of morbidity and death for cancer patients. Despite the improvements in detecting and treating the primary ovarian tumor, current therapies against metastasis are still limited. Dysregulated HGF/c-Met signaling of cell migration has been suggested to contribute to tumor invasion and metastasis. Specific inhibitors against HGF/c-Met signaling, therefore, may have important therapeutic potential for the treatment of cancers in which Met activity contributes to the invasive/metastatic phenotype. Recently, several c-Met receptor antagonists have been developed. The goal of the proposed research is to investigate the effects of a c-Met specific ATP-competitive small-molecule SU-11274 on human ovarian carcinoma cell growth, scattering, and transendothelial invasion. This team hypothesizes that inactivation of c-Met by SU-11274 treatment may significantly decrease growth rate, scattering efficiency, and transendothelial invasive activity in ovarian cancer cells expressing high levels of activated c-Met. The project will be facilitated by the use of electric cell-substrate impedance sensing (ECIS), a novel cell-based biosensor that monitors morphological changes of cells adherent on small gold electrodes. This approach will be combined with the team's established ability in fluorescence imaging and digital image analysis to characterize a variety of cellular responses to SU11274. The specific aims are as follows:

1. To determine the effect of c-Met inactivation on HGF-induced growth and scattering of ovarian carcinoma and normal cells
2. To examine the effect of c-Met inactivation on the transendothelial invasion of ovarian cancer cells.

The proposed research will provide new information regarding the functional role of activated c-Met in metastatic behaviors of human ovarian carcinoma cells. The results will clarify the feasibility of using SU-11274 as a potential therapeutic target for ovarian cancer and the possible toxicity of SU-11274 on normal HOSE cells. It is also designed to test the ECIS's capability of evaluating the invasive potential of ovarian cancer cells. It will explore the possibility of using the ECIS system to analyze potential drugs for their abilities to suppress metastasis, particularly at the level of transendothelial invasion.

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The results will contribute to a broader goal of developing a new molecularly targeted anti-cancer therapy for ovarian cancer and possibly other forms of cancer.