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**Could a Repurposed HIV Drug Stop the Spread of High-Grade Ovarian Cancer Cells?**

**Grantee:** Pamela K. Kreeger, PhD (need headshot)

**Institution:** University of Wisconsin (North Region)

**Area of Focus:** Mission Boost

**Grant Term:** 1/1/2019 to 12/31/2020

**The Challenge:** No current treatments focus on managing the actual spread of the disease. High-grade serous ovarian cancer (HGSOC) metastasizes when cancer cells move from the primary tumor into fluid in the abdominal cavity and then attach to mesothelial cells that line abdominal organs. Changes in the immune system can make this easier.

A type of immune cell called macrophages release MIP-1b. MIP-1b triggers mesothelial cells to make a protein known as P-selectin. Under a previous ACS grant, the lab of Pamela K. Kreeger, PhD, found that mesothelial cells with more P-selectin are "stickier'' for tumor cells. The study confirmed that HGSOC patients have higher levels of MIP-1b and P-selectin.

**The Research:** The drug maraviroc blocks the effects of MIP-1b. The FDA has approved it for the treatment of HIV. Now Kreeger's team is testing how well maraviroc slows tumor progression and recurrence using mice that have been transplanted with human HGSOC tumor tissue.

Her lab is also analyzing samples of blood, excess abdominal fluid, and tissue from newly diagnosed HGSOC patients to identify biomarkers. Measurements of P-selectin or MIP-1b levels in blood or fluid might accurately reflect tissue levels of P-selectin in mesothelial cells.

Stage II of this grant is a pilot study of patients with HGSOC to check that they can take maraviroc without problems and that it's effective at lowering their P-selectin level.

**The Goal and Long-term Possibilities:** The long-term goal for Kreeger is a clinical trial of maraviroc. The drug may reduce complications from metastatic tumors and improve survival in patients with either initial or recurrent HGSOC. Kreeger also hopes to develop an easier way to monitor P-selectin levels in tissue.

**ORIGINAL**

The spread of a tumor from its original site to other organs in the body is known as metastasis. While for many tumor types metastasis is accomplished by travel through the blood or lymphatic systems, metastatic high-grade serous ovarian cancer (HGSOC) results from the dispersion of tumor cells from the primary tumor into the peritoneal fluid. After traveling through this fluid, the tumor cells must attach to the mesothelial cells that line abdominal organs; however, mesothelial cells function to prevent organs from sticking to each other and are therefore non-adhesive. Despite this barrier, HGSOC patients are frequently diagnosed with extensive metastases, leading to complications such as bowel obstructions.

Under the previous ACS grant, our lab analyzed how changes in the immune system that accompany tumor development impact the ability of cancer cells to attach to mesothelial cells during metastasis. Through our research, we determined that a type of immune cell called macrophages secrete MIP-1b, which acts on mesothelial cells to induce production of a protein known as P-selectin. That increase in P-selectin then makes the mesothelial cells ‘stickier'' for tumor cells. We have confirmed that HGSOC patients have increased MIP-1b and P-selectin, suggesting that this mechanism could be targeted to slow or stop metastasis.

Therefore, under Stage I of the Mission Boost we propose to use a mouse model of HGSOC to test the effect of inhibiting MIP-1b on tumor progression and recurrence. Specifically, we will test the effect of maraviroc, an FDA-approved drug that inhibits the receptor for MIP-1b. We will also expand our analysis of HGSOC clinical samples to identify biomarkers for this process. Successful completion of Stage I will lead to a Stage II pilot study to confirm that maraviroc is tolerated by HGSOC patients and effective at decreasing their P-selectin level. Combined, a successful Stage I and II would motivate a prospective clinical trial to determine if maraviroc can improve progression-free survival or overall survival in patients with initial or recurrent HGSOC.