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**Using the Body's Natural Killer Cells to Fight Ovarian Cancer**

**Grantee:** Melissa Geller, MD (need headshot)

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

**Area of Research:** Clinical Cancer Research, Nutrition, and Epidemiology

**Grant Term:** 1/1/2015 to12/31/2019

**The Challenge:** Standard treatments for recurrent ovarian cancer work for fewer than 1 in 5 women. Limitations uncovered in a promising Phase II clinical trial of natural killer cell IV infusions in ovarian cancer patients has led this team headed by Melissa Geller, MD, back to the lab.

**The Research:** Natural killer (NK) cells are a key part of the human immune system. They can recognize and kill many types of tumor cells, including ovarian cancer. For example, trials have shown dramatic anti-tumor effects when particular NK cells from healthy donors are transferred into patients with leukemia.

Geller's team — which combines expertise in stem cell biology, immunotherapy, and gene therapy — is using adult stem cells to grow NK cells that target mesothelin, an "ID tag" on ovarian cancer cells. They test lab cells and tumor samples to make sure the NK cells work. Then they see how the targeted NK cells work in mice compared to NK cells grown without the target and usual NK cells found in blood.

The researchers are also evaluating the combination of targeted NK cells boosted by a drug that shuts down an enzyme that interferes with anti-tumor immune responses.

**The Goal and Long-term Possibilities:** Because NK cells are the first responders of the immune system, the hope is that they can attack different subtypes of tumors to create a "universal" treatment for women with ovarian cancer. The results from Geller's laboratory study can be directly applied to the ongoing clinical trial.

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Current standard therapies for recurrent ovarian cancer provide a dismal (<20%) response rate. There is an urgent need for novel therapeutic strategies, as most women with relapsed ovarian cancer will die of progressive disease. Here, we will advance a novel cellular immunotherapy that can provide a targeted “universal” cell population to treat women with ovarian cancer. We propose to test an innovative treatment for advanced ovarian cancer that uses natural killer (NK) cell-based immunotherapy–an approach with the potential to substantially improve patient outcomes. NK cells are a key part of the human immune system with the ability to recognize and kill diverse types of tumor cells, including ovarian cancer. In clinical trials at our institution, dramatic anti-tumor effects have been seen with cytokine activated NK cells from healthy donors that are transferred into patients with leukemia. We recently completed a Phase II trial of intravenous NK cell infusions in ovarian cancer patients. Although the approach is promising, we have identified limitations. It is these limitations that have led us back to the laboratory as recent significant advances have demonstrated the efficacy of targeted immune therapy using NK cells. We will produce a targeted NK cell population highly effective against human ovarian cancer and investigate the ability to use this therapy to cure refractory cancers. We will use a pre-clinical mouse model to test the combination of the targeted NK cells plus a drug that inhibits an enzyme known to play a key role in suppressing anti-tumor immune responses. We hypothesize this combination will increase killing of ovarian cancer cells in vivo to produce a markedly increased therapeutic response. This laboratory study will be directly translatable into our clinical trial and will maximize anti-tumor efficacy of NK cells in ovarian cancer. Thus, we propose a translational study that will combine expertise in stem cell biology, immunotherapy, and gene therapy to provide a novel and desperately needed therapy for women with ovarian cancer. Our findings are expected to have a significant positive impact not only on the field of ovarian cancer, but also in other solid tumors.