

American Cancer Society – Institutional Research Grants 2015

“Photoacoustic Molecular Imaging of Ovarian Cancer”

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Background: Screening for ovarian cancer in high risk women is rational because the disease is treatable in early stages, but very deadly in late stages. CA125 testing and transvaginal ultrasound imaging have encouraging metrics including sensitivity and specificity of 89.4% and 99.8%, but have positive predictive values below 50% and are insufficient for use in the general population.

Objective/hypothesis: Folate binding proteins are highly expressed in ovarian cancer; hence, these targets can be used to increase the specificity and sensitivity of ovarian cancer screening. My central hypothesis is that nanoparticles targeted to the folate receptor will increase tumor signal and contrast above background greater than non-targeted nanoparticles—this will increase the sensitivity and specificity of screening. Because folate receptors are expressed on the cell surface, it is critical to use a contrast agent that leaves the vasculature. My expertise is in nanoparticle imaging agents that do just that—these contrast agents are built from the clinically approved indocyanine green and poly-lactic-coglutamic acid. I will now use them for ultrasound-based molecular imaging of ovarian cancer.

Specific aims: I will image folate binding proteins with both conventional ultrasound and novel photoacoustic ultrasound that combines the high contrast of optical imaging with the resolution of ultrasound. I will evaluate the performance metrics of both through the following steps.

Step 1. We will make the nanoparticles via an emulsification process.

Step 2. We will add a cloaking polymer and folate.

Step 3. We will validate the contrast agent with cell culture experiments.

Step 4. We will image an orthotopic model of human ovarian cancer.

Study design: I am only seeking one year of pilot funding and thus these aims will build on my prior work in chemistry, animal models, and imaging.

1. Create contrast agents.
2. Functionalize contrast agents with targeting ligands.
3. Validate targeting specificity with cell culture.
4. Image an orthotopic mouse model of human ovarian cancer.

The final imaging step has four groups of animal subjects: 1) animals with untargeted nanoparticles to study non-specific binding, 2) animals with targeted contrast agents to study specific binding, 3) competitive inhibition of in vivo binding sites to validate target specificity, and 4) imaging tumors from different cell lines to illustrate discrimination between different biomarker expression levels.

Cancer relevance: This contrast agent is capable of imaging folate receptor with both ultrasound and photoacoustic imaging. These modalities have profound advantages over the optical methods previous used for folate including better depth of penetration and better temporal/spatial resolution. Ultrasound already provides excellent anatomical information, and the small size of nanoparticles facilitates imaging the sensitive and specific biomarkers present on the cell surface. Although deployed here for ovarian cancer, this imaging agent will have broad utility across many cancer types. This work is also easily reconfigurable to other imaging targets as they emerge in the literature. Pilot clinical trials in ovarian cancer patients can begin after this work, and I will seek additional funds from the NIH at the conclusion of this project, e.g. PAR-13-185 and PAR-13-189.