Project 4: Use of 3D Quantitative Optical Methods to Optimize Mebendazole Treatment of Ovarian Cancer

ABSTRACT

Effective treatment for recurrent epithelial ovarian cancer is a major, unmet public health need as the response rates of the patients are often low with the traditional chemotherapy. Repurposing drugs is an increasingly popular strategy in oncology due to the financial and logistical constraints of new drug development. Recently, anti-parasitic drugs such as mebendazole have surfaced as repurposed oncology drugs and showed promise in treating multiple types of tumors. The anti-parasitic drugs, fenbendazole and mebendazole, are in the benzimidazole class and have been FDA-approved to treat pinworm and other helminthic infections in humans and animals for decades. The selectivity of these drugs for the parasite rather than the host is explained by irreversible blockade of glucose uptake in the parasite, leading to glycogen depletion and degeneration of the endoplasmic reticulum with eventual cell death. In addition, both fenbendazole and mebendazole inhibit microtubule polymerization and function in parasites but not in humans or mammals, owing to differential key residues, which create an inaccessible hydrophobic pocket to which the anti-parasitic drugs cannot bind. Although these seem to be the mechanisms of action in parasites, the exact mechanism of their anti-cancer effect in human cells is unknown. In order to investigate this issue, we **hypothesize** that by measuring and quantifying changes of tumor morphology, vasculature, and density using the combination of two novel high-resolution tissue imaging methods including optical coherence tomography (**OCT**) and fluorescence laminar optical tomography (**FLOT**), drug mechanism of action and therapeutic effects can be accurately assessed *in vivo*. The primary objective of this project is to thoroughly evaluate the anti-cancer effects of anti-parasitic drugs in an ovarian cancer mouse model using OCT and FLOT. In order to validate our hypothesis and realize the objective of this project, we propose the following three specific aims. **Aim 1:** To optimize calibration of intraperitoneal post-necropsy tumor measurements in an ovarian cancer xenograft mouse model treated with mebendazole using OCT and FLOT compared to standard electronic caliper measurements. **Aim 2:** To use OCT and FLOT to characterize changes in blood vessel morphology upon exposure of an ovarian cancer xenograft mouse model to mebendazole treatment. **Aim 3:** To use OCT and FLOT to measure superficial versus deep tumor cell death and identify quantitative imaging markers for evaluating efficacy of mebendazole-based anti-cancer treatment. If successful, the results of this project will provide important information regarding anti-cancer effects of mebendazole and also the convinced preliminary or pre-clinical data to support the research project leader (**RPL**) to apply for a more comprehensive project (*i.e.,* **NIH R01** or **DOD CDMRP** Level 2 grant) to further investigate and determine the optimal mechanism of applying this promising anti-parasitic drug to more effectively treat epithelial ovarian cancer in the clinical study or trial involving human subjects.