Lipoprotein Omega-3 Fatty Acid Nanoparticles:
A Novel Treatment for Breast Cancer Liver Metastases

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This year alone in the United States nearly a quarter million women will be diagnosed with breast cancer. Approximately, one-third of breast cancer patients develop metastatic disease and about half of these women will have breast cancer spread to the liver. Breast cancer metastasis to the liver is a serious complication of breast cancer that is often associated with poor patient outcome. Invading breast tumors in the liver often impair liver function and diminish the drug eliminating capacity of the liver. As a result, dosing of systemic chemotherapies is limited and cancer treatments are delivered at suboptimal potencies allowing breast cancer lesions to progress unabated. Hence, preservation of liver function is critical in breast cancer management. Currently, there are a number liver-directed therapies that can alleviate the tumor burden within the liver, including surgery or locoregional treatments such as thermal ablation, stereotactic body radiotherapy and radioemboliztion with Yttrium-90. Unfortunately, each of these therapies comes at the cost of damaging the normal adjacent liver. An ideal liver-directed therapy would selectively eradicate liver tumors while sparing neighboring normal liver tissue and function. In this grant proposal, we offer a new approach to treating metastatic liver tumors that should greatly improve our ability to manage breast cancer. We plan to take advantage of the sensitivity of breast cancer cells to the natural omega-3 fatty acid, docosahexaenoic acid (DHA). Unlike standard chemotherapy drugs, DHA kills cancer cells at doses that do not injury normal cells. In this project, we aim to locally deliver DHA to metastatic breast cancer cells in the liver using a natural cholesterol carrying protein from our blood called low-density lipoproteins (LDL). We have modified LDL to carry DHA omega-3 fatty acids, instead of its natural cholesterol cargo. The LDL-DHA is ideal for this treatment because breast cancer cells are known to take up large amounts of LDL. Hence, in many ways LDL-DHA will act as a classic "Trojan Horse". Breast cancer cells actively acquire LDL expecting nutrients and resources to promote their rapid tumor growth, but instead the LDL-DHA delivers a toxic payload that elicits their demise. Thus, we propose that locoregional delivery of LDL-DHA can be used to treat the breast cancer metastasis in the liver without injury to the surrounding normal liver. This would be an effective treatment for all patients with breast cancer liver metastasis, in particular, this therapy may even be curative for those patients with breast cancer metastasis confined to the liver (5% of patients with metastatic breast cancer). In this proposal we will first assess the ability of the LDL-DHA to bind, be taken up and kill a panel of human breast cancer cells. Secondly, animal studies in rats with breast cancer liver metastasis will be carried out to determine the effectiveness of LDL-DHA treatment in selectively killing breast cancer metastasis without injuring the surrounding normal liver. These early preclinical studies will be fundamental in demonstrating the feasibility of this innovative treatment strategy and providing preliminary data necessary for clinical translation of this therapy.