

# A Pre-Clinical Model of anti-HER2/neu-Antibody Reactive Breast Cancer Metastases

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Only about one in five women survive 5 years after receiving a diagnosis of widespread metastatic breast cancer. The liver is one of the most frequent sites of metastases and the cause of death in most of these situations is liver failure. Liver metastases are resistant to almost all currently available breast cancer treatments. Many treatments that seem to work in animal studies show disappointing results in humans. One of the reasons for this is that most of the animal studies use reduction in the size of tumors growing on the mouse body surface. Since breast cancer becomes very difficult to treat after it has metastasized, animal models that imitate metastatic dissemination of cancer are essential to adequately evaluate new treatments. In particular, such models should follow a metastatic pattern that is also seen in patients. We have considerable experience developing and using animal models of breast cancer metastases. In this grant proposal, we seek support to develop and characterize a metastatic mouse model whose metastases express the receptor target HER2/neu. Such a model would allow us to test a very potent type of radiation (alpha-particles) directed against widely disseminated tumor cells. This would be done by intravenously administering a cancer-cell homing molecule that is tagged with an isotope that emits alpha-particles. The efficacy and toxicity of this type of "guided missile" approach against metastatic breast cancer is best evaluated using an animal model that leads to widespread metastases, including liver metastases. The receptor target that will be expressed by our proposed metastatic model will allow us to use drugs that are already approved for clinical use such as trastuzumab (Herceptin®) and pertuzumab (Perjeta®). This would make it much easier and faster to get approval to use this type of treatment in patients should studies using the metastatic animal model show that the treatment with targeted alpha-particles is safe and effective. The model and any cancer cell lines that we generated will be available to the cancer research community and we plan on publicizing the utility of this model for studies with other treatments.