Patient-derived tumorgrafts as personalized predictors of therapeutic response for metastatic breast cancer

Background and Rationale

In order to make progress in understanding the biology of breast cancer, and to develop new drugs against the disease, we must find ways to experiment with tumor cells in the most physiologically relevant way possible. The most common method is to grow the cells on a plastic dish, as tissue cultures. However, we now know that growing tumor cells in isolation, outside of their normal environment, causes changes in the behavior and genetic make-up of the cells that could lead to misinterpretation of results. Many of these changes are irreversible and accumulate with time, which raises concerns about using the common breast cancer cell lines, which have been cultured for decades, to guide state-of-the-art breast cancer research.

Growing human breast cancer cells in mice avoids many of the problems that occur in cultures, and allows for collection of more reliable data. The presence of normal cells in the environment around tumors is known to play a role in cancer behavior, so using a whole animal system is ideal. It is also the only way to study the process of metastasis, where the tumor spreads from the breast to other organs and is the cause of 90% of breast cancer deaths. The most common models for breast cancer research and drug discovery are made by injecting these cancer cell lines into mice. Thus, the irreversible genetic and behavioral aberrancies that arose in culture remain, resulting in models that are poor predictors of drug effectiveness. In reality, how well represented is any given patient's tumor in the current cell line models? Wouldn't it be fantastic to be able to test each patient's tumor individually for susceptibility to particular therapies, in a clinically relevant setting?

We have taken the latter approach and generated exciting new models of breast cancer, where tumors are taken directly from patients and grafted into mouse mammary glands. These "tumorgrafts" are remarkably representative of the original tumors from the patient, including in their ability to metastasize, and we have generated tumorgrafts for all of the major types of breast cancer. Now, a critical objective is to determine whether tumorgrafts are reliable predictors of a tumor's actual response to therapy in the patient, which is the objective of this proposal.

Objective

This proposal, over the course of one year, seeks to fulfill one major objective: to test the value of tumorgrafts in predicting response to therapy. Since patients with metastatic breast cancer often live with their disease for extended periods of time, we envision a future where we can use the tumorgraft system to determine optimal, personalized therapeutic regimens for patients by prospectively testing drug combinations in mice carrying that patient's tumor.

Potential impact of the proposed research on patients with metastatic breast cancer

All new drugs must go through pre-clinical testing in animal models prior to clinical trials. The ability to improve predictions of drug efficacy with dependable models will bring the most promising new drugs or drug delivery modalities to the clinic. Our tumorgraft models are particularly exciting because they are individualized, and recapitulate the original tumor remarkably well, particularly with respect to metastasis – the real problem in breast cancer. The concept of "personalized medicine" is coming closer to fruition. What if every patient could have her own tumor grown in mice, in order to test which drug(s) will be most effective? Or, what if we could determine that her cancer will not progress, so she could avoid unnecessary chemotherapies? Of course, these approaches are currently too costly and far-reaching to be reality for every patient, but our proposal seeks to pave the way in determining whether such concepts are achievable. If funded, the current proposal will allow us to harness a tangible opportunity that may change how breast cancer research is translated to the clinic.