Microvascularized 3D Breast Cancer Constructs for Drug Testing and Development

Describe the proposed research idea (1,000 character limit):

The **goal** is to develop *microvascularized* three-dimensional (3D) breast cancer constructs that closely model the complex cellular interactions and biology of breast cancer and will better predict in vivo response than current pre-clinical models. The proposed constructs are designed for use in drug development and for the prediction of individual patients' responses to therapies (i.e., personalized medicine). Central to the constructs is the presence of endothelial cell-lined, continuously perfused microchannels to overcome diffusion limitations for long term growth and for drug delivery. The constructs will consist of a novel carbon particle scaffold for structural support, which is embedded in basement membrane material containing breast cancer cells and stromal cells, and will be perfused by a bioreactor. The constructs intended for drug development will be representative of ER+, basal and Her2+ subtypes. Constructs for selecting individual patient's therapies will include cells from dissociated breast cancer tissues. The ability of the constructs to serve as models for evaluation of drug delivery and therapeutic response will be assessed.

Describe the potential impact of the proposed research and how it is innovative (2,000 character limit).

Potential Impact:
Cancer drug development is a long and expensive process. Many new molecular entities start the development process, but the number that ultimately proves successful in clinical trials is small. A major factor contributing to this low success rate is the lack of preclinical models that accurately predict effectiveness. In addition, with the advent of molecularly targeted therapies, there is a need for better prediction of sensitivity and resistance of individual cancers to specific therapies. The long-term goals for the proposed constructs are 1) to utilize them for more predictive, rapid, and cost effective drug development and 2) for predicting an individual's response to therapies. These constructs also offer the possibility of using endpoints other than cytotoxicity, such as angiogenesis or invasion, for evaluation of drug effectiveness. The ability to maintain these models over a long duration will allow testing of sequential administration of drugs and the targeting of residual cells that are resistant to initial drug therapies. These novel microvascularized models have the potential to transform drug development and therapeutic testing by being more biologically relevant and, thereby, providing more accurate predictive endpoints.
Innovation:
The major innovations of the 3D constructs are 1) the presence of micron scale, endothelialized and continuously perfused microchannels to promote cell viability for long term culture and better drug delivery, 2) the inclusion of cancer epithelial cells, fibroblasts and endothelial cells, all of human origin, to more closely recapitulate the cellular complexity and microenvironment of breast cancers, 3) the inclusion of patient's breast cancer tissues in constructs for predicting an individual's response to specific therapies, 4) the use of a novel scaffold material, a carbon particle aerogel, that was developed by our collaborators at Southern Research, a major drug discovery institute with extensive resources for drug validation and testing. In addition, the integrated expertise of our multidisciplinary team adds innovation. There is expertise in the areas of breast cancer, clinical pathology, fibroblast-epithelial interactions, matrix biology, bioengineering and the fluid mechanical effects of vascular cell development.