Benjamin Solomon – Research Proposal

Project Title: 3D engineered breast cancer tissue at varying stiffness on a micro- and nanoscale platform for the assessment of metastatic migration and candidate pharmaceuticals

Tumor microenvironment (TME) by itself is a complex structure which comprises of cancer cell, stromal cells, immune cells, and other sub-cell types with a unidirectional supply of nutrition. 2D conventional invitro systems fail to recapitulate the native tumor microenvironment and their stiffness at local heterogeneity which leads to a poor correlation for determining the efficacy of a newly developed drug at a preclinical phase. On the other hand, there are very few established 3D invitro tumor models which implicate the relation between cell-matrix, cell stromal interactions under the influence of biological, mechanical, and physiological cues which are major contributors of creating a TME with varying stiffness. To accelerate the process of drug approval for cancer treatment at the preclinical phase we need a better in vitro tumor model which can mimic the stiffness and cancer cells behavior similar to the native microenvironment providing all the above features.

The use of biomaterial-based invitro cancer tissue formation has been a classical method in recapitulating the native tissue microenvironment. Nonetheless, these materials are limited to studies showing how stiffness can influence the tumor invasiveness and progression that has proximity to the invivo stiffness. Also, there is a lack of strong mechanical cues and a dynamic physiological condition that entirely mimics the microenvironment. For this reason, the development of the tumor-on-a-chip platform is an essential asset in identifying the key mechanism of cancer invasion, cell-stromal interaction, cell-matrix interaction and investigate the different metastatic cascade. This platform will also help in finding the correct dosing of an oncolytic agent specific to the cancer cell and its ECM stiffness.

For my study, I am proposing to 1.) Validate a hybrid polymer material PEG-Fb (Polyethylene glycol - fibrinogen) - Polyethylene glycol diacrylate (PEGDA) covalently crosslinked with fibrinogen which is the extracellular matrix (PEG-Fb). Engineering 3D breast cancer tissues with MDA-MB-231 cells with BJ5ta fibroblast cells using this biomaterial, we can investigate the stiffness and correlate with the native tumor tissue at locational heterogeneity (Core, Midpoint and Periphery). Invitro stiffness will be compared with a mouse model (NCR nude mice) injected with MDA-MB-231 cells 2.) Incorporate the PEG-Fb-laden breast cancer tissue within a tumor-on-a-chip platform and investigate the metastatic ability of breast cancer cells when cocultured with a stromal component. The chip design I will work is created by using a scanned mouse vasculature designed with AutoCAD to fit a primary tumor chamber where the tissue formation takes place and an empty secondary and tertiary tumor chambers for monitoring metastasis. The vasculature surrounding the tumor area will be seeded with the appropriate endothelial cells to mimic the inner lining of the blood vessels. 3.) Assess the engineered tumor co-culture cells within the microfluidic chip for various genetic and molecular expression changes that correlate to the invivo tumor. Cells will be collected every 5 days and RNA will be isolated for monitoring the genetic changes of the stemness, proliferation, and metastatic markers. 4.) Validate the tumor-on-a-chip platform for Patient-derived xenograft model derived from different stages of colorectal cancer cells engineered with Peg-Fb (PDX CRC). PDXCRC from Stage 2 (Non-Metastatic), Stage 3b (Partially metastatic), and (stage4 Highly Metastatic). A comparison of each metastatic progression will be monitored and compared to a cell line to argue the importance of xenograft models which will better recapitulate the native TME.