in vitro and *in vivo* gels applied to cancer metastasis, drug responses, and dormancy

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Improved *in vitro* models are needed to better understand cancer progression and bridge the gap between *in vitro* proof-of-concept studies, *in vivo* validation, and clinical application. Many methods exist to create biomaterial platforms, including hydrogels, which we use to study cells in contexts more akin to what they experience *in vivo*. Our lab has multiple approaches to create such biomaterials, based on combinations of poly(ethylene glycol) (PEG) with peptides and zwitterions. In this presentation, I will discuss our findings in using these cell culture environments to understand the role of the extracellular matrix (ECM) in controlling cancer cell innate drug response via adaptive signaling. Specifically, I will present data comparing the behavior of breast, prostate, and ovarian cancer cells to chemotherapy and targeted drugs when cultured as 3D spheroids, on 2D gels, and as a function of the stiffness of the tumor microenvironment. This approach uncovered that cells on 2D hydrogels and spheroids encapsulated in 3D hydrogels were less responsive to receptor tyrosine kinase (RTK)-targeting drugs sorafenib and lapatinib, but not cytotoxic drugs, compared to single cells in hydrogels and cells on plastic. We found that transcriptomic differences between these in vitro models and tumor xenografts did not reveal mechanisms of ECM-mediated resistance to sorafenib. However, a systems biology analysis of phospho-kinome data uncovered that variation in MEK phosphorylation was associated with RTK-targeted drug resistance. Using sorafenib as a model drug, we found that co-administration with a MEK inhibitor decreased ECM-mediated resistance in vitro and reduced in vivo tumor burden compared to sorafenib alone. In sum, we provide a novel strategy for identifying and overcoming ECM-mediated resistance mechanisms by performing drug screening, phospho-kinome analysis, and systems biology across multiple biomaterial environments. Our work suggests that different model systems are important for evaluating cell response to receptor tyrosine kinase inhibitors, whose efficacy depends on cell-ECM interactions.