

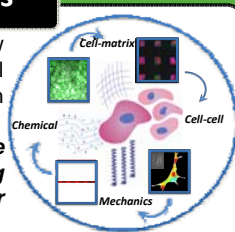
# Heterotypic tumor models to study breast cancer under pathologically relevant conditions

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## Therapeutic Developments

\$800 million is spent in the development of each new anticancer drug as >70% of new compounds fail in animal models and clinical trials despite showing promise in preclinical testing.

**Improved tumor models for preclinical testing are necessary to decrease cost. By utilizing engineering approaches the 3D microenvironment can be better mimicked in vitro.**



## Breast Cancer Screening

Often, breast tumors are first noticed by either the patient or physician during manual palpation of the breast as a hard lump (fig. 1). Tissue density which correlates with stiffness can be seen on mammograms which are used to identify abnormalities indicative of cancerous tissue (fig. 2).



Figure 1 (left): Self-breast exams as well as yearly physician exams are often the first route of detection of breast tumors. (from: www.umm.edu)

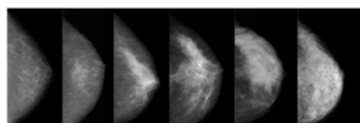
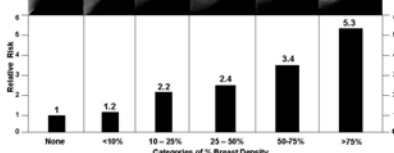


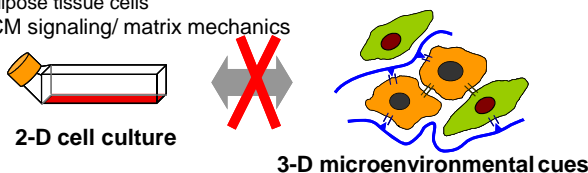
Figure 2 (right): Increasing breast tissue density, as seen by mammograms, has been correlated with an increased risk for development of breast cancer. (from: Boyd, N.F., et al., Breast Dis, 1998, 10(3-4): p. 113-26.)



## Development of Tumor Models

Currently, preclinical testing is performed in 2-D tissue culture. 3-D models will better mimic the tumor microenvironment:

- Heterotypic cell interactions native to breast tumor
  - Breast Tumor Cells
  - Adipose tissue cells
- Cell-ECM signaling/ matrix mechanics



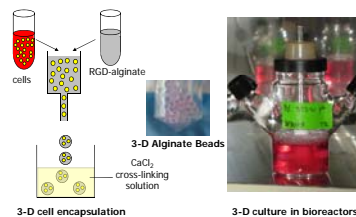
- In vivo tumor**
- Breast Tumor Cells
  - Adipose Tissue Cells
  - Cell Adhesion Sites
  - ECM Stiffening
  - Cell Integrins

- In vitro model for Preclinical testing**
- MDA-MB231
  - 3T3-L1
  - RGD peptide
  - Alginate hydrogel
  - Cell Signaling

**These models will better recapitulate in vivo tumor signaling to allow for better preclinical testing prior to animal models.**

## Drug Testing in Improved Tumor Models

### a.) Mimicking the Tumor in 3-D



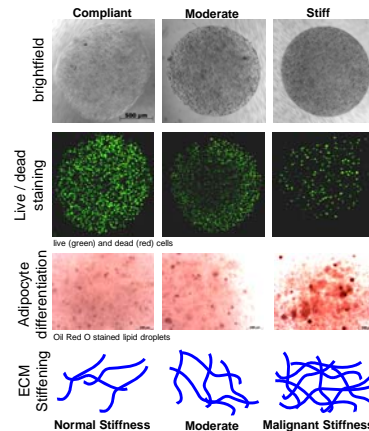
Cells inherent to the breast tumor microenvironment can be seeded within alginate hydrogels mimicking the malignant and normal tissue stiffness (a).

Both cell types remain viable within these hydrogels; however, the differentiation of progenitor cells is decreased with increasing ECM stiffness (b).

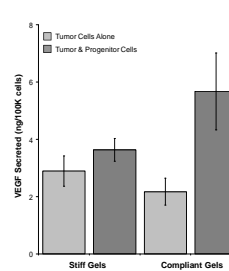
Tumor cells responsiveness to chemotherapeutics is decreased in 3-D culture (c).

Cell interactions between the tumor cells and the progenitor cells alter the behavior of each cell type (d - i, ii, iii).

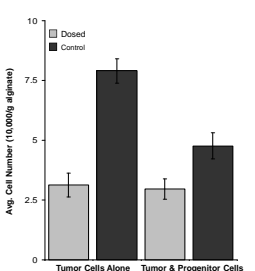
### b.) Cell viability and differentiation



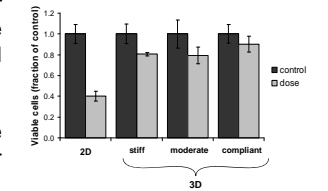
#### i. Increased Angiogenic Potential



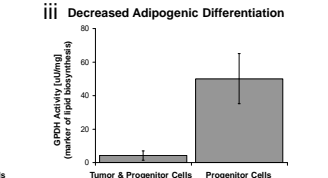
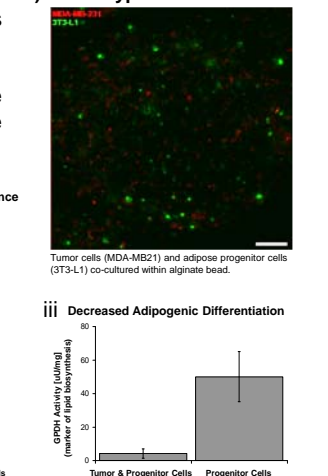
#### ii. Increased Chemotherapeutic Resistance



### c.) Tumor Cell-Matrix Interactions



### d.) Heterotypic cell interactions



## Conclusions

- This would be a superior model to use for drug testing in the Pharmaceutical Market.
- Responsiveness of breast tumor cells is dramatically reduced by 3-D culture and in the presence of adipose progenitor cells.
- Improved models of the cell-cell and cell-matrix interactions in tumors are necessary to provide improved preclinical testing methods prior to animal and human testing.

## Acknowledgements

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## High Throughput Drug Testing

- Refine 3-D tumor models; i.e., develop 3-D co-cultures to evaluate whether increased stiffness at the breast cancer/adipose tissue interface indirectly modulates drug responsiveness by altering adipose cell behavior.
- Develop platform for high-throughput drug testing

