A novel breast-cancer model of early stage invasion

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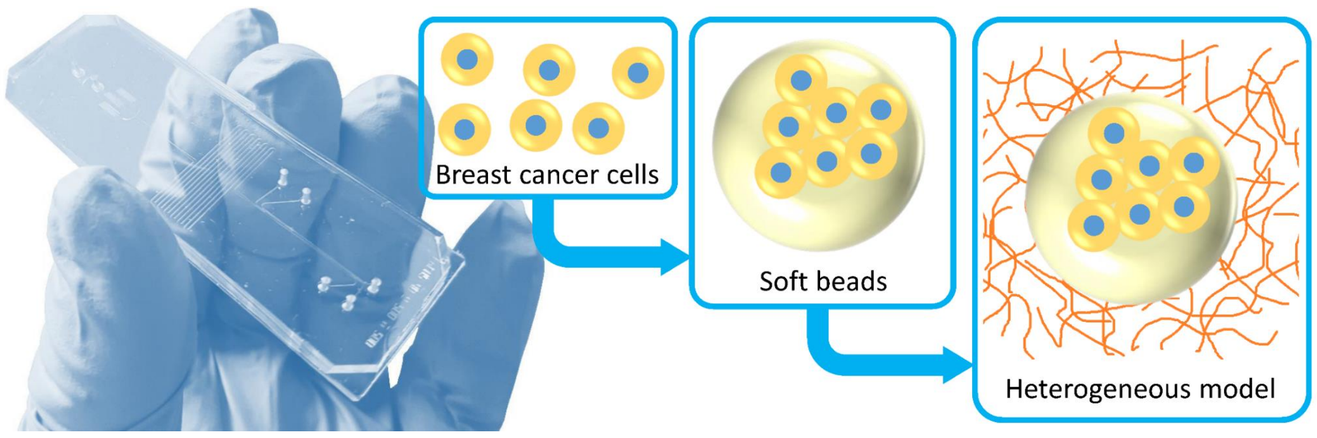
Using microfluidic methods to mimic a heterogeneous physical tumor microenvironment

Jelle J. F. Sleeboom[1,2,3]
Cecilia M. Sahlgren[2,3,4]
Jaap M. J. den Toonder[1,3]

[1] Microsystems group, TU/e
[2] Soft Tissue Engineering & Mechanobiology, TU/e
[3] Institute for Complex Molecular Systems, TU/e
[4] Turku Centre for Biotechnology, Åbo Akademi and Turku University

The majority of breast cancer deaths are not caused by the primary tumor, but by metastasis to other organs [1]. However, the mechanisms that underlie the first stage of metastasis, the invasion of cancer cells into surrounding tissue remain elusive, due to the complexity of the cellular, biochemical, and biophysical interactions in cancer tissue.

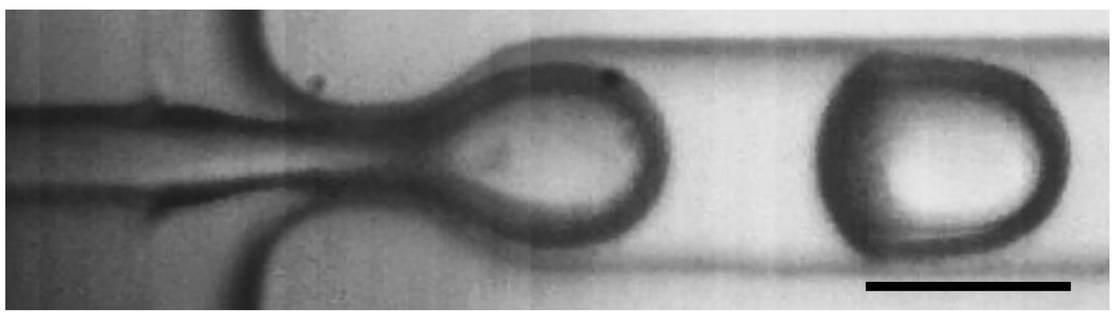
In this work, we propose a novel *in vitro* breast cancer model that focuses on dissecting the influence of the biophysical properties of the extracellular matrix (ECM) on the onset of cancer invasion. Based on microfluidic technology, it will provide us with the necessary tools to independently vary different material and cell properties, while it provides the cells with a physiologically relevant environment.



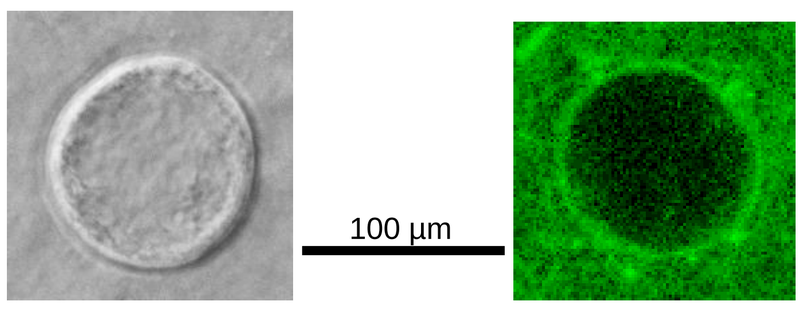
The key biophysical property this model captures is the heterogeneous ECM composition before invasion: Initially, cancer cells reside in a soft basement membrane before invading the fibrous and stiffer stromal ECM [2]. A microfluidic bottom-up fabrication approach enables the generation of this environment.

Model fabrication

First, MDA-MB-231 cells are encapsulated in Matrigel beads that mimic the basement membrane. Next, the beads are embedded in a collagen I hydrogel, mimicking the stromal extracellular matrix.



Cell encapsulation in Matrigel droplets using a microfluidic flow-focusing device. The scale-bar indicates 100 µm.

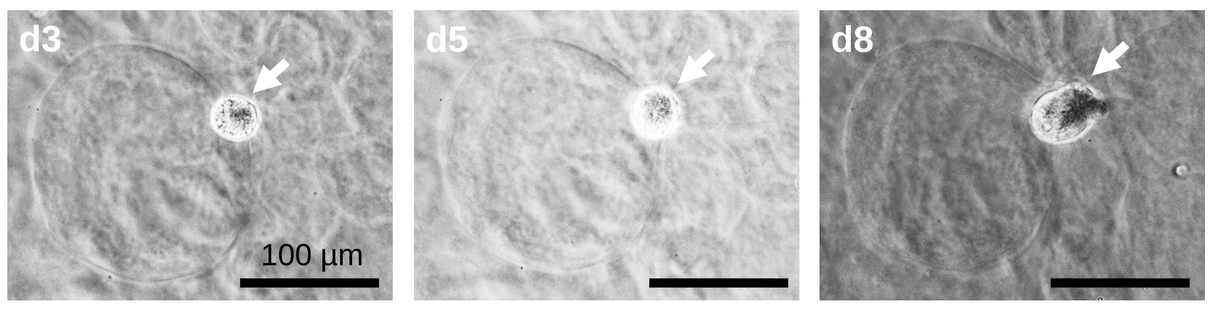


A single Matrigel bead embedded inside a collagen I matrix in a bright-field (left), and a confocal image (right) labelled with a CNA35-OG probe for collagen.

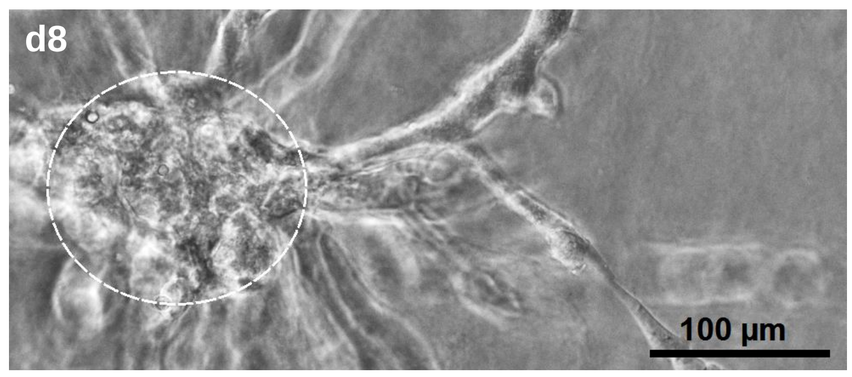
By generating these micro-tissues using droplet microfluidics, many controlled cancer models can be generated in a high throughput fashion, while systematically changing parameters like ECM structure and composition, tumor size, and inclusion of different cell types.

Cancer invasion

We observe different types of invasion into the stromal ECM compartment: clusters of cancer cells invading the stromal collagen matrix, and complete invasion by proliferating cancer cells.



An invading cluster of MDA-MB-231 breast cancer cells, imaged on day 3, 5, and 8 after establishing the model



A fully invading tumor model at day 8, originating from the area circled in white

Further development is aimed towards integration of control over physical parameters such as the stiffness, and development of quantitative analyses of the cell invasion process.

[1] Aceto, N., et al. (2014). Circulating tumor cell clusters are precursors of breast cancer metastasis. Cell, *158*(5), 1110–1122.
[2] Yu, H., et al. (2011). Forcing form and function: Biomechanical regulation of tumor evolution. Trends in Cell Biology, 21(1), 47–56.