Cancer intravasation-on-a-chip : a LEGO house for tumors!

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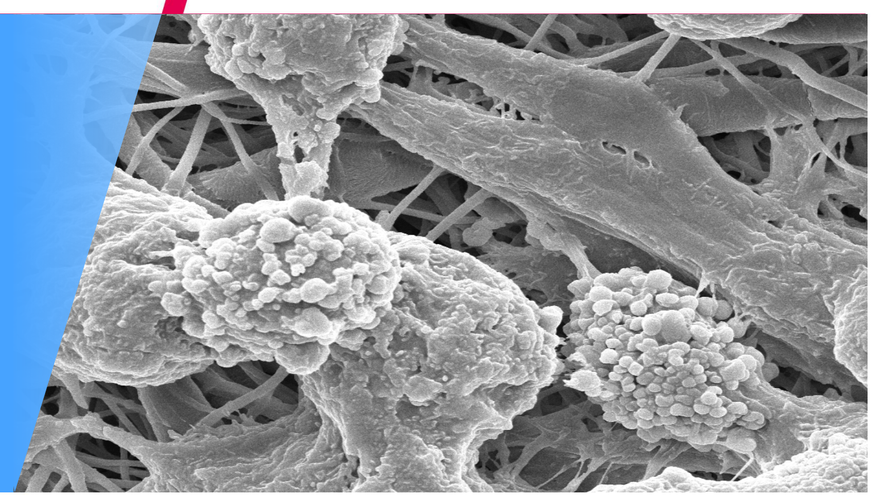
A LEGO house for tumors!



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What is cancer intravasation?

The process where cancer cells *leave the primary tumor* and *invade to the blood vessel*. As shown in figure 1, intravasation is highly regulated by the micro-environment of the tumor. An important component of the micro-environment is the extracellular matrix (ECM) which can be seen as the building structure of a LEGO house.

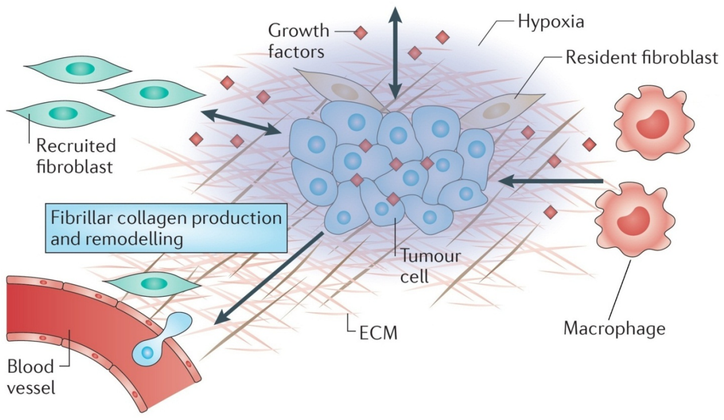

Figure 1 – Schematic of cancer intravasation [1]. Cancer cells are in continuous cross talk with their micro-environment to invade to the blood.

Why a LEGO house?!

A proper model for cancer intravasation requires a proper model for the micro-environment, or in other words, a right LEGO house for cancer cells to live in! To model the process, microfluidics is used because there is:

- more control on the biochemical content,
- less human error by automating the experiments,
- more complex designs,
- and less ethical issues, it is a LEGO house!

The **GOAL** is

to study how the *mechanical properties* of the *extracellular matrix* regulate the *tumor intravasation* by using a *microfluidic chip*.

Multidisciplinary road

For the production of our LEGO house we drive on a *multidisciplinary road*. It starts with building the structure (steps 1 and 2), but it does not mean that the cancer cells would feel at home (steps 3 and 4), like *in vivo*. Furthermore, the road is two-way, meaning each step gives us a feedback to further modify the micro-environment we try to mimic. Driving in the multidisciplinary road is a challenging task which requires knowledge of many engineering disciplines and biological aspects

Step 1 - ECM fabrication

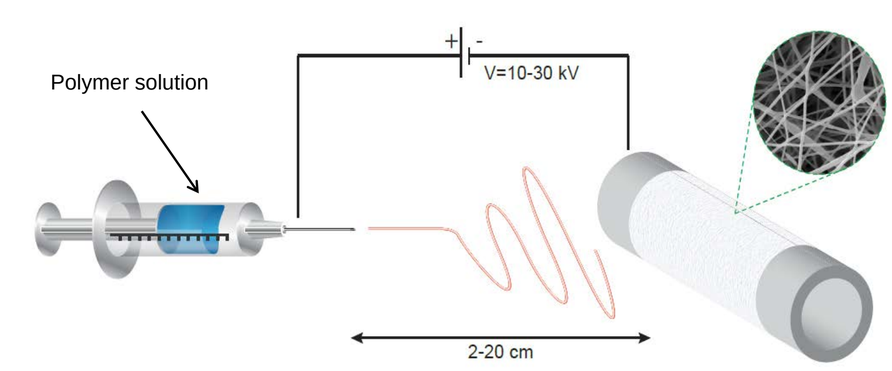

Figure 2 – Overview of electrospinning process[2]. With this process, fibrous scaffolds can be fabricated with different stiffness and fiber diameters. For the start, Poly-caprolactone (PCL) is used as the material. However, in the future, PCL will be replaced by natural proteins.

Step 2 - Chip fabrication

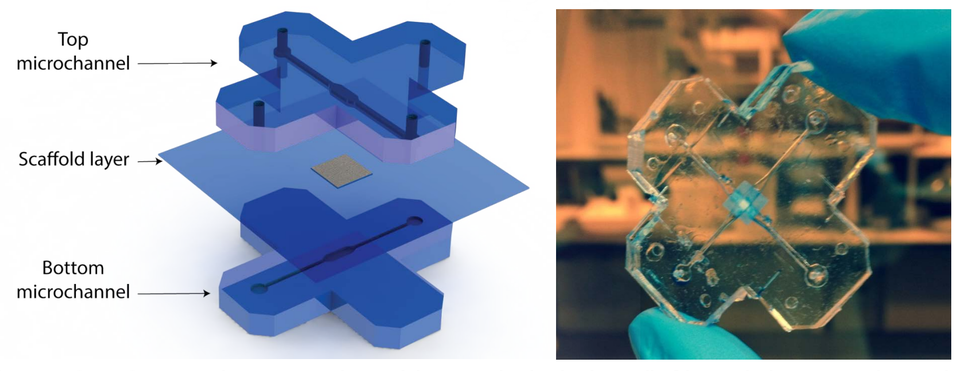

Figure 3 – Cancer intravasation chip, exploded view (left) and the complete chip (right). The chip is made of PDMS through a process called “selective curing”. It consists of two microchannel layers and a scaffold carrier layer. The fabrication process is robust and flexible for different scaffolds with different thickness.

Step 3 - Cell culturing

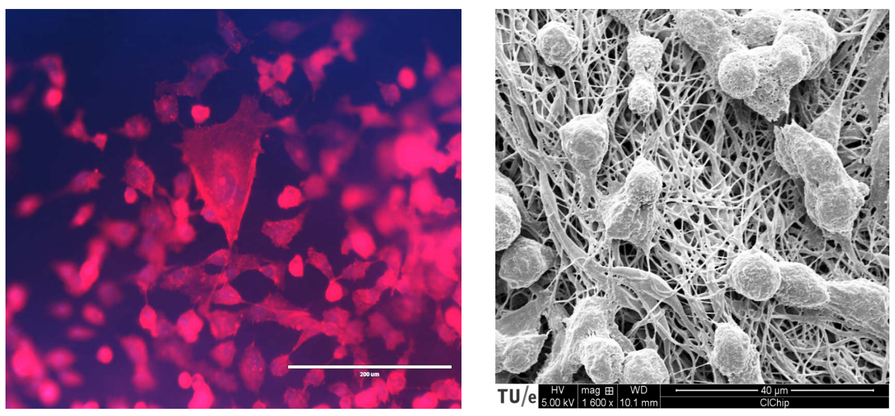

Figure 4 – Breast cancer cells in the chip with the viability of more than 95% after 7 days. A special feature of the new fabrication process is the direct access to the cells for further analyses, such as high quality fluorescence imaging (left) and scanning electron microscopy (right).

Step 4 - Biological assay

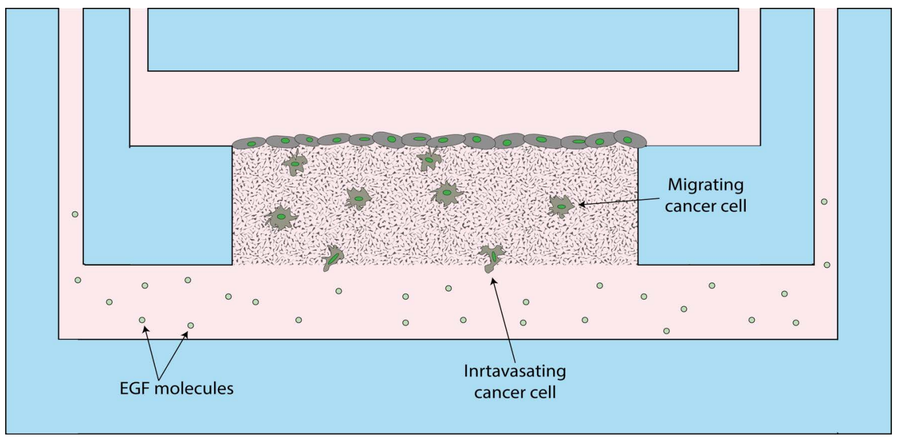

Figure 5 – Chemotaxis assay; Cells are cultured in the upper channel and Epidermal Growth factor (EGF), a chemo-attractant, is introduced to the lower. As a result, a 3D migration model through the fibrous scaffold is created.

Conclusion

We have fabricated PCL electro-spun scaffolds, and also developed a new fabrication method to integrate the scaffold inside a microfluidic chip. We have cultured breast cancer cells in the chip. In the future, chemotaxis assay will be tested for different geometry and stiffness of the ECM.

[1] Gilkes, Daniele M., Gregg L. Semenza, and Denis Wirtz. "Hypoxia and the extracellular matrix: drivers of tumour metastasis." *Nature Reviews Cancer*14.6 (2014): 430-439.
[2] Paul Miggiels, MSc thesis, Microsystems group, department of Mechanical Engineering, Sep 2015.

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