

Metastasis on Chip: Modelling Invasive Breast Cancer Cells

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BACKGROUND

Breast cancer is the greatest cause of mortality for women globally according to the world health organization (WHO) [1], with **metastasis** serving as the main contributing factor. The severe impact of metastasis can be attributed to a lack of understanding of the mechanisms at play in the early stages of the metastatic cascade, specifically **invasion** into the stroma and intravasation into the blood capillaries, processes where the invasive and subsequently **circulating tumor cells (CTCs)** go through a number of **phenotypic changes** with unknown effects on cancer treatment [2]. Most cancer treatments focus on the proliferative feature of cancer, disregarding the low responsiveness and side effects that these drugs have on these cells.

In view of the above, we aim to study the effect of **doxorubicin (DXR)**, a first-line anthracycline chemotherapeutic agent for breast cancer treatment [3], on the distinct phenotypes established within the breast cancer-invasive microenvironment. For this purpose, we used an MDA-MB-231 spheroid embedded in collagen I to model the extracellular matrix of an invasive solid breast tumor, with the prospective of integrating the model in a microfluidic device with physiologically relevant physicochemical stimuli to better recreate the invasion.

RESULTS

MDA-MB-231 are more resistant to DXR when already invaded the matrix

To study DXR effect in the initial metastatic stages, two breast cancer models were established: a **primary carcinoma** model ("early detected tumor") treated from the beginning of the experiment and an **invasive carcinoma** model treated after the invasion ("metastatic breast cancer tumor").

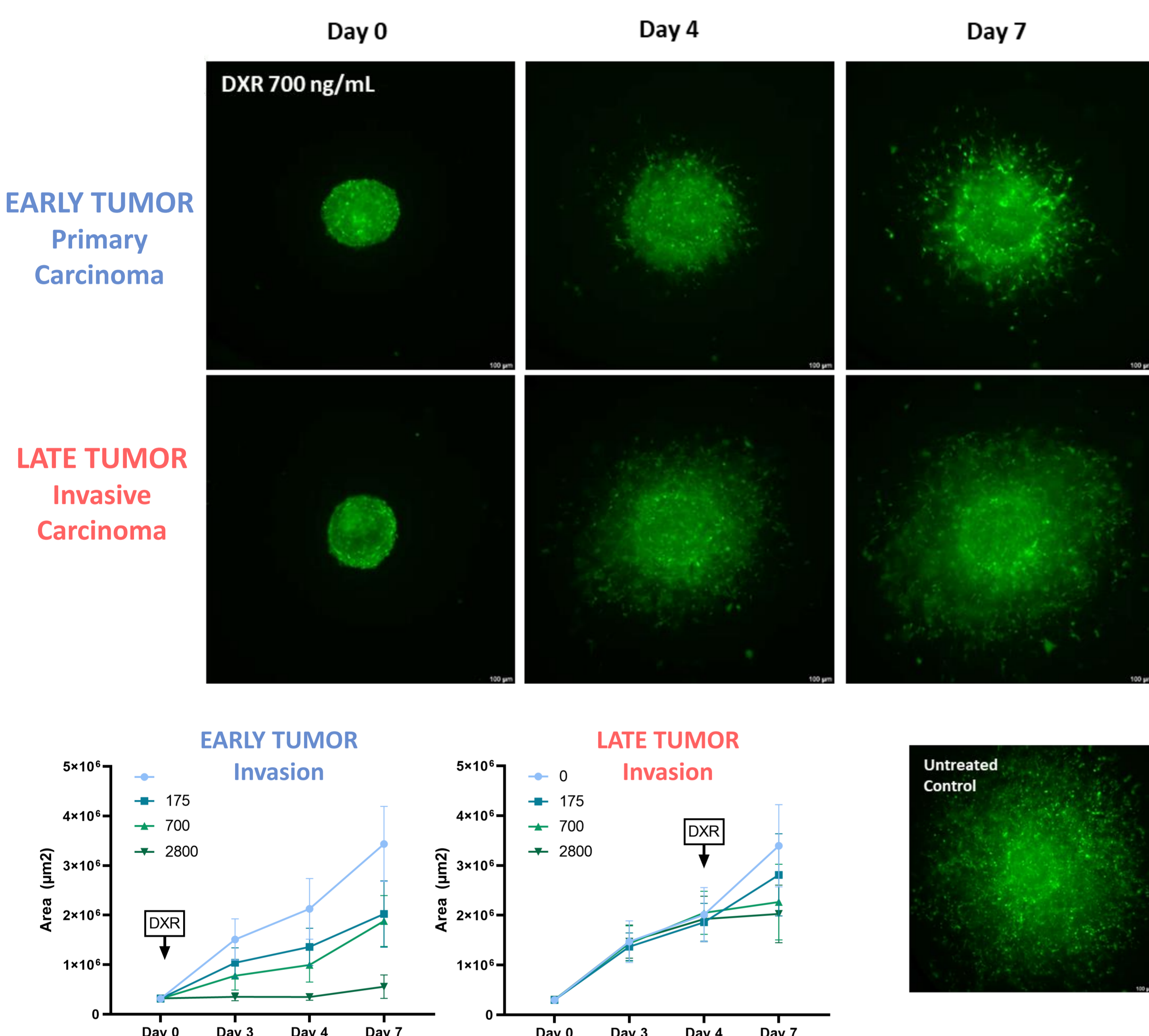


Figure 1. Visual comparison of invasion of the breast cancer models. The progression of the invasion area of each DXR-treated group (0, 175, 700 and 2800 ng/mL) is shown in the complementary graphs.

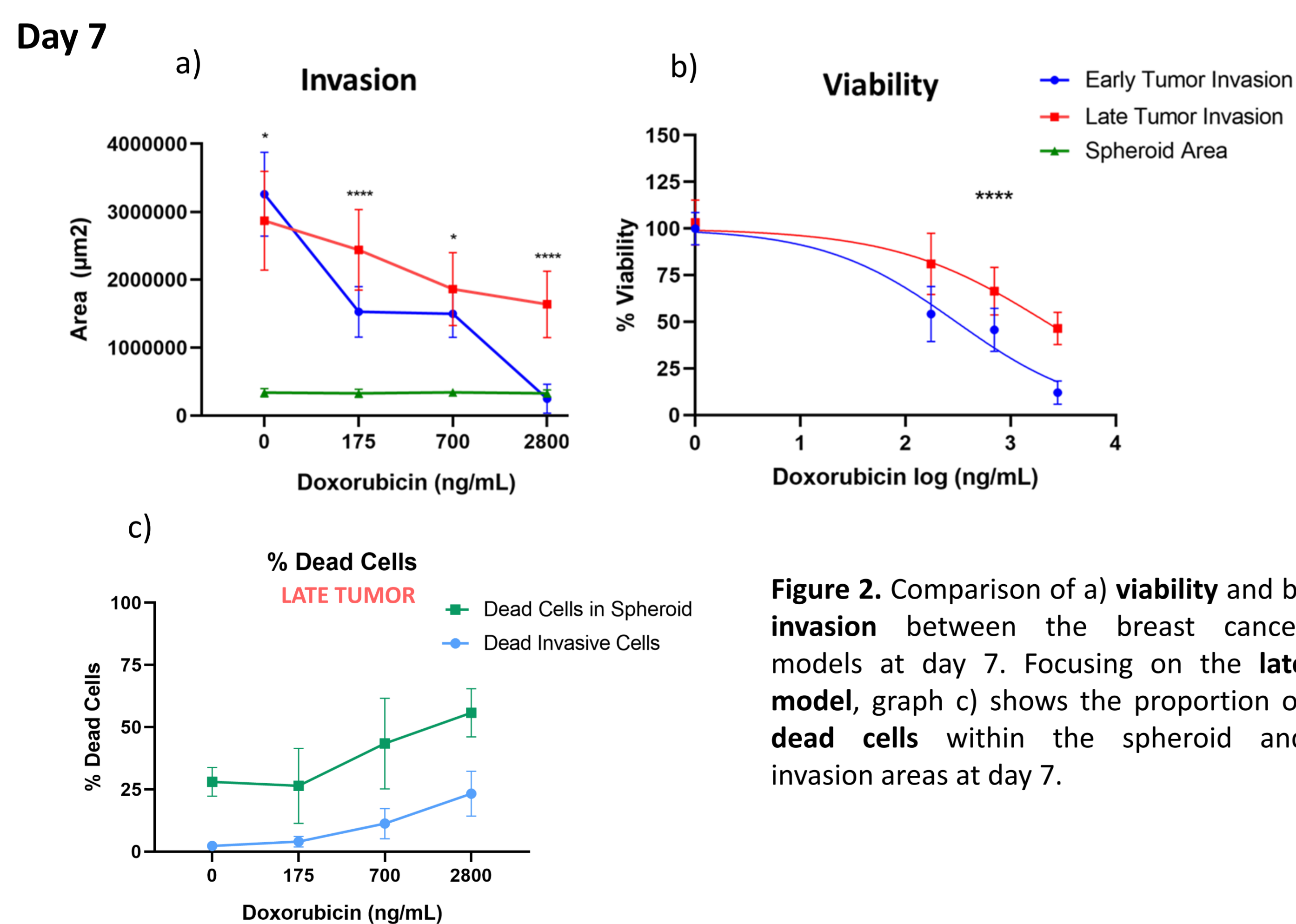
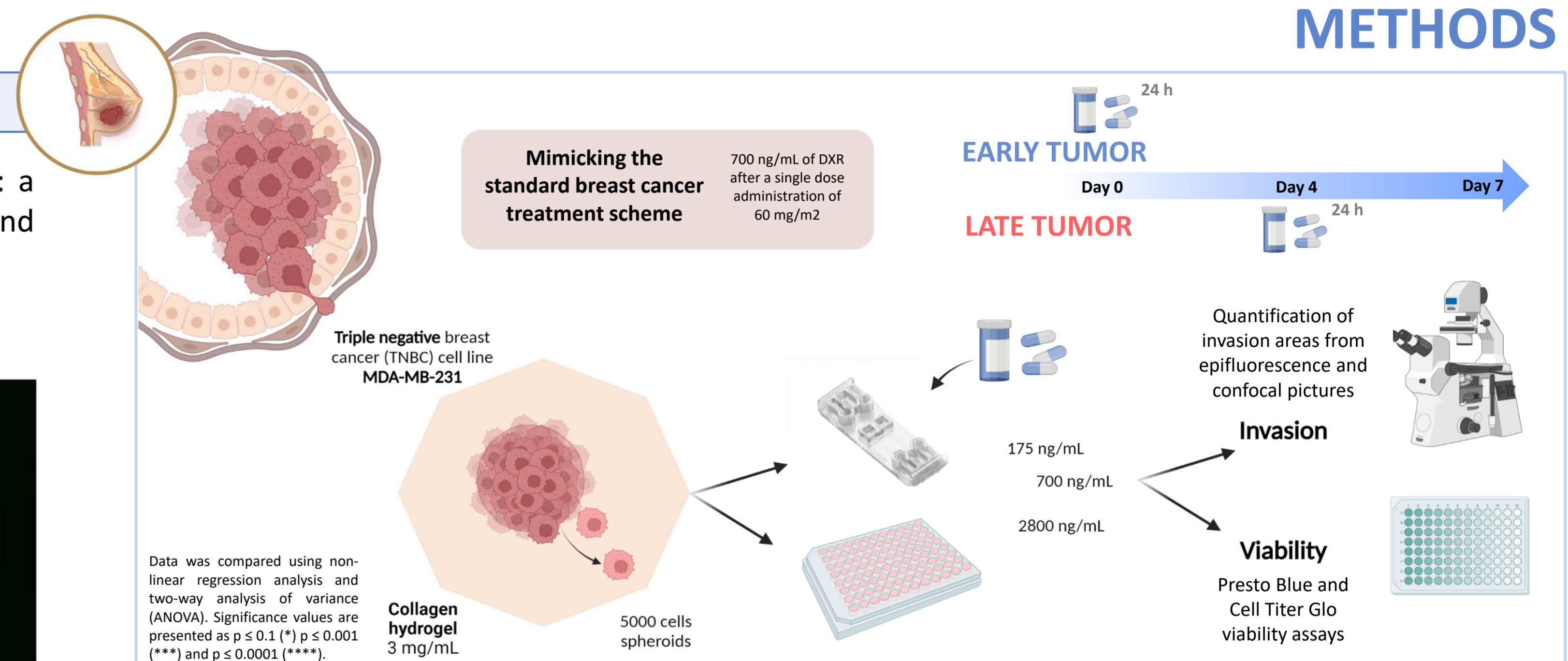


Figure 2. Comparison of a) **viability** and b) **invasion** between the breast cancer models at day 7. Focusing on the **late model**, graph c) shows the proportion of **dead cells** within the spheroid and invasion areas at day 7.

CONCLUSIONS

This work allows the obtention of a simple breast cancer invasive model for drug evaluation with a closer look at invasive cells response and evasion mechanisms. The model has been able to reproduce physiological sensitivity to doxorubicin while confirming 3D culture and invasive cells resistance. Considering this, as well as the potential for integrating the model with a microfluidic chip, this model is useful to explore the mechanisms of breast cancer progression and invasive cell resistance.

METHODS



MDA-MB-231 are more resistant to DXR when cultured in 3D

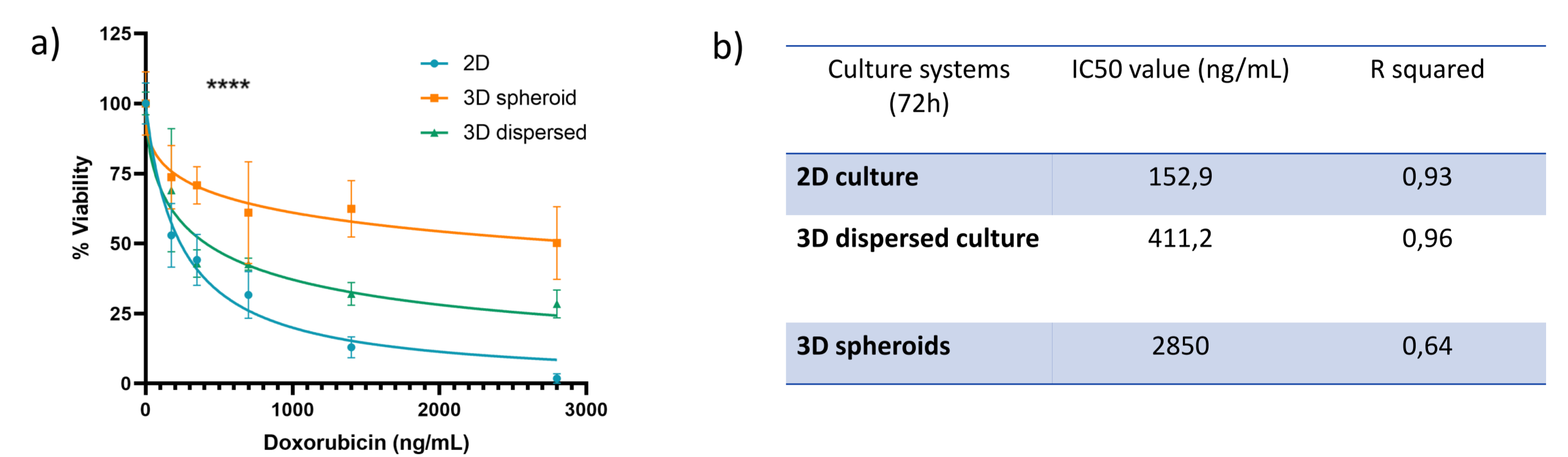


Figure 3. The **viability** of MDA-MB-231 cells cultured in adherent 2D, embedded inside a collagen matrix and forming spheroids is presented in graph a). **IC50 values** for each curve are shown in chart b).

MDA-MB-231 invasion can be enhanced on a microfluidic chip

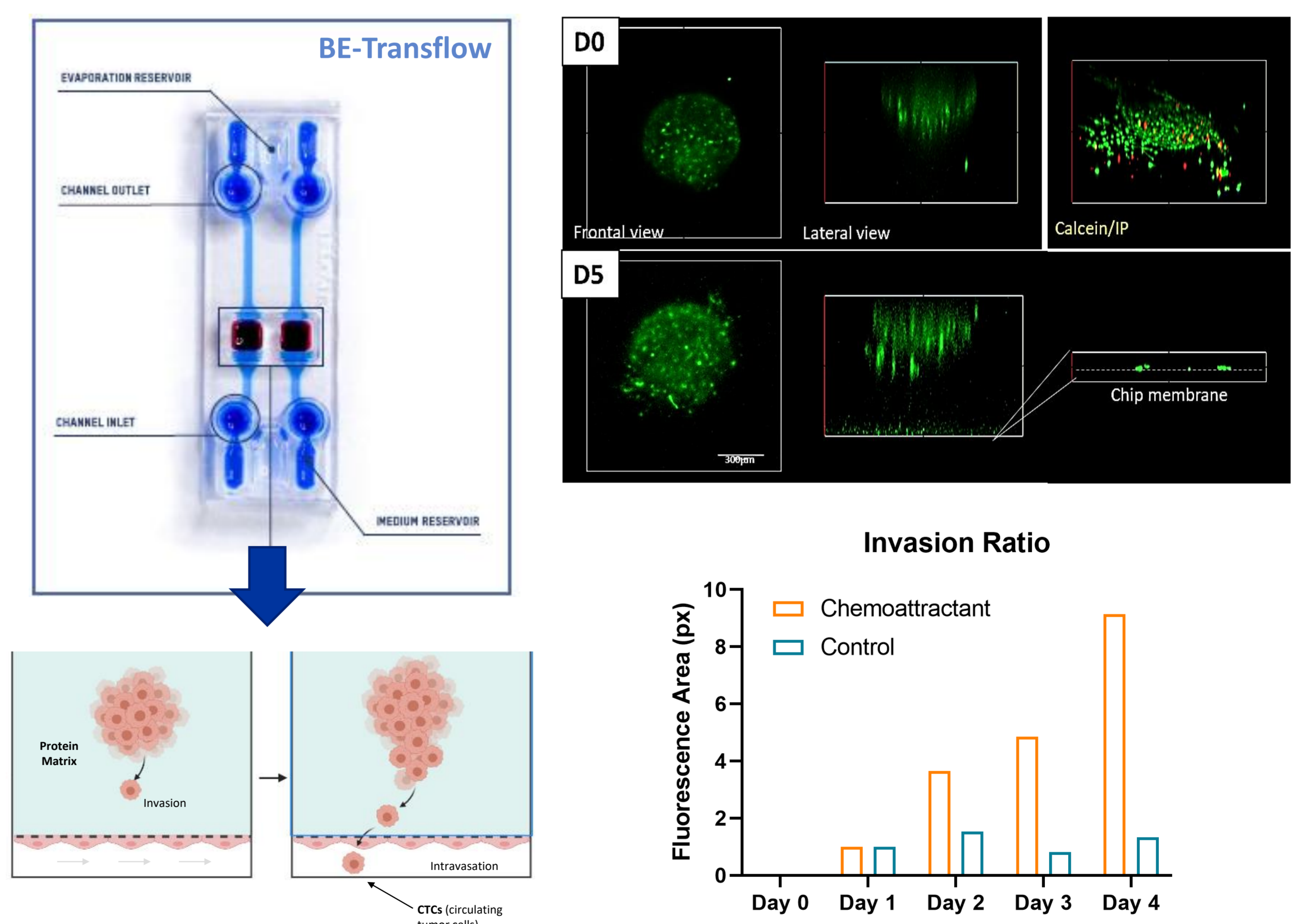


Figure 4. Schematic representation of the breast cancer invasive model inside of the BE-Transflow well.

Figure 5. Evolution of the **early breast cancer model** over 4 days. The fluorescence area represents the number of cells invading the collagen hydrogel under the spheroid.

REFERENCES

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Financial support from Moore4Medical project (ECSEL program) is gratefully acknowledged. Authors wish to thank also the support from the Government of Aragón (DGA) and the Spanish Association Against Cancer (AECC).