Patient-derived scaffold (PDS) – recapitulating relevant tumor microenvironment features for preclinical drug testing

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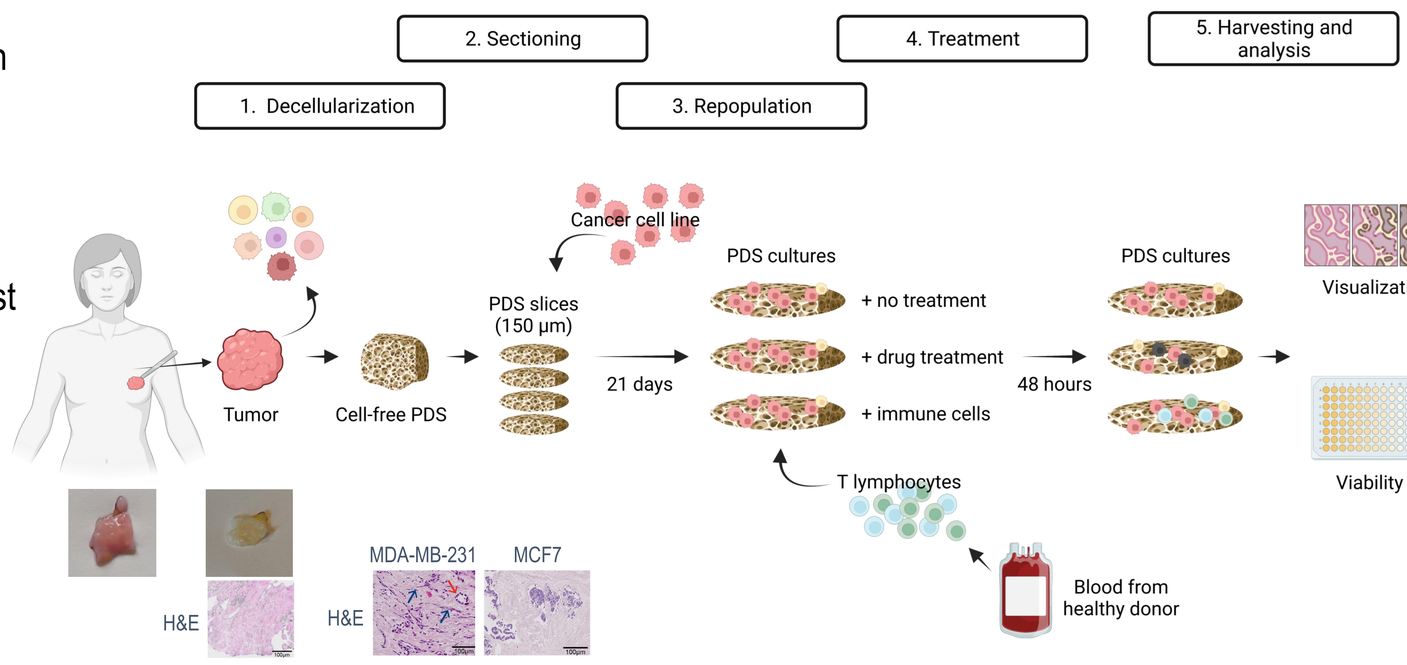
Introduction

The interplay between cancer cells and other components of the tumor microenvironment (TME) plays an important role in disease progression, metastasis and drug resistance. For better understanding of this interactions and the influence of individual patient cancer microenvironments in tumor prognosis and drug response, we have:

- Developed an *in-vivo* like model from patient breast cancer tissue (PDS).
- Analysed intrinsic factors in PDSs linked to clinical characteristics of the original cancer.
- Evaluated the PDS suitability for drug and immune therapy testing.

Methods and work-flow



PDSs induced-gene expression changes in response to chemotherapies are associated with clinical parameters and disease progression from the original tumor

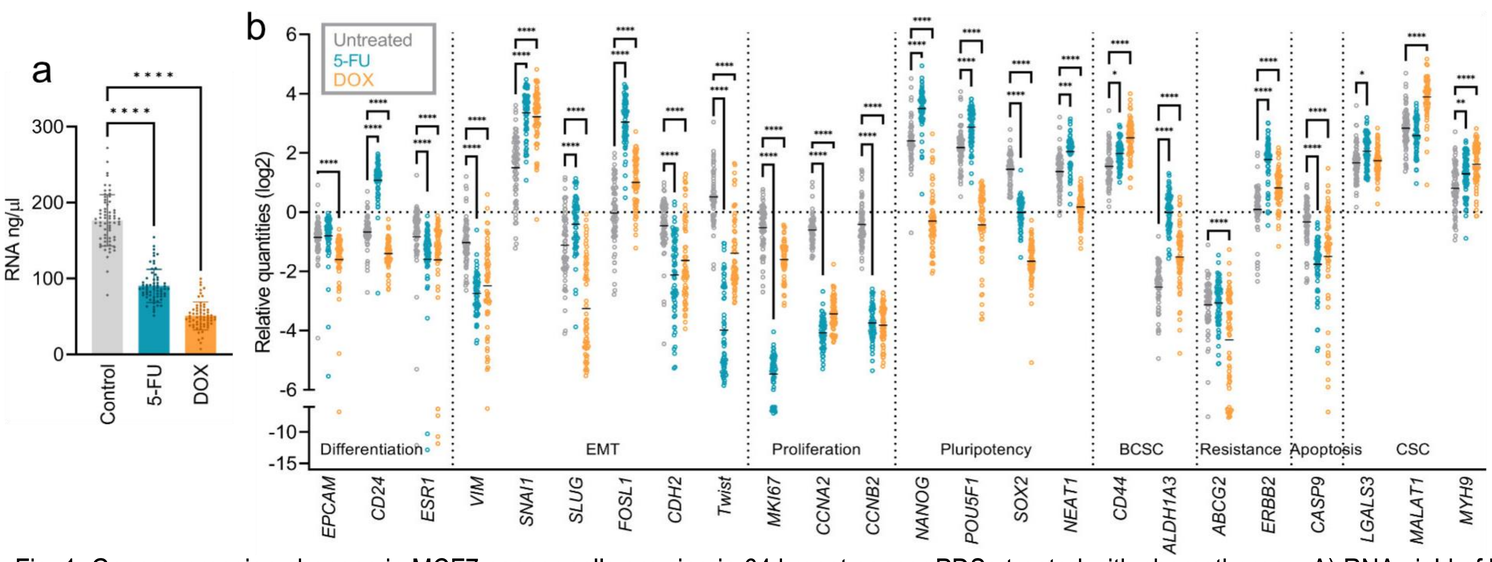


Fig. 1. Gene expression changes in MCF7 cancer cells growing in 64 breast cancer PDSs treated with chemotherapy. A) RNA yield of lysates from PDS cultures. B) Scatter plots showing gene expression levels of untreated and treated PDS cultures, relative to untreated 2D culture. Individual PDSs represented by dots. Controls (untreated), 5-fluorouracil (5-FU) or doxorubicin (DOX)

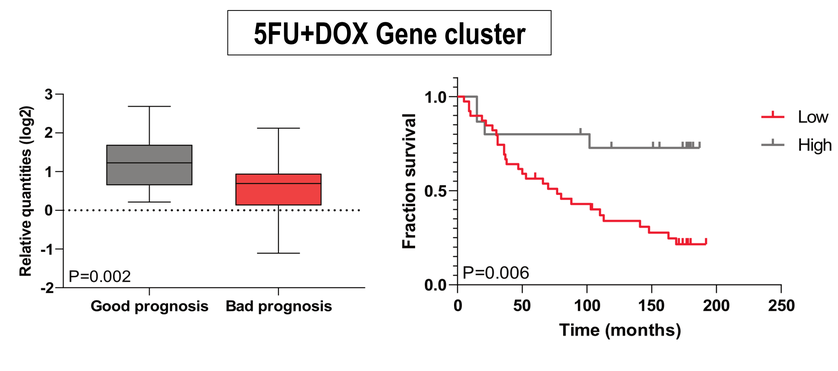


Fig. 2. Bar plot and Kaplan-Meier plot of a cluster of genes significantly associated to prognosis in both treatments, 5FU and DOX. Low expression of the gene cluster in MCF7 cancer cells growing in PDSs after treatment with 5-FU and DOX was associated to poor prognosis of the patients.

Drug repurposing: CSC low proliferative PDS-induced phenotypes during FDA-approved drugs screening matched *in vivo* experiments

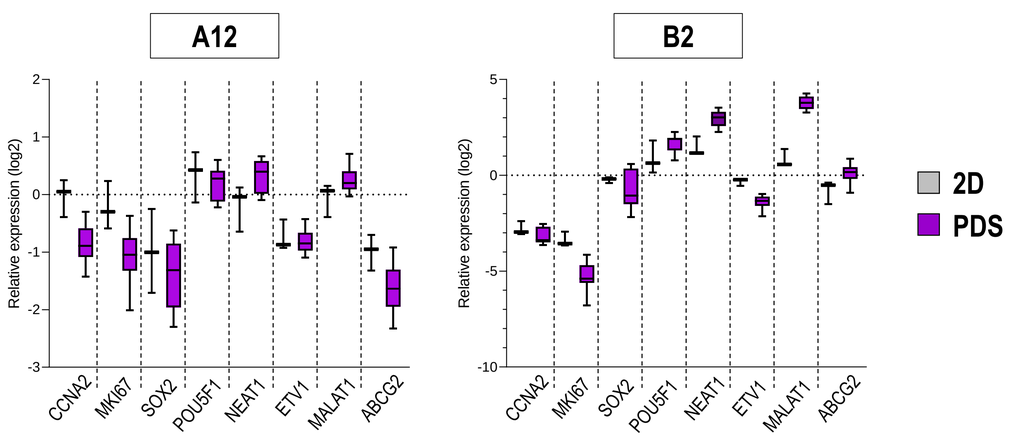


Fig. 3. In contrast to 2D cultures, the treatment with B2 increased the expression of pluripotency and CSC related genes in MDA-MB-231 breast cancer cells growing in PDSs. Relative gene expression to non-treated samples is shown.

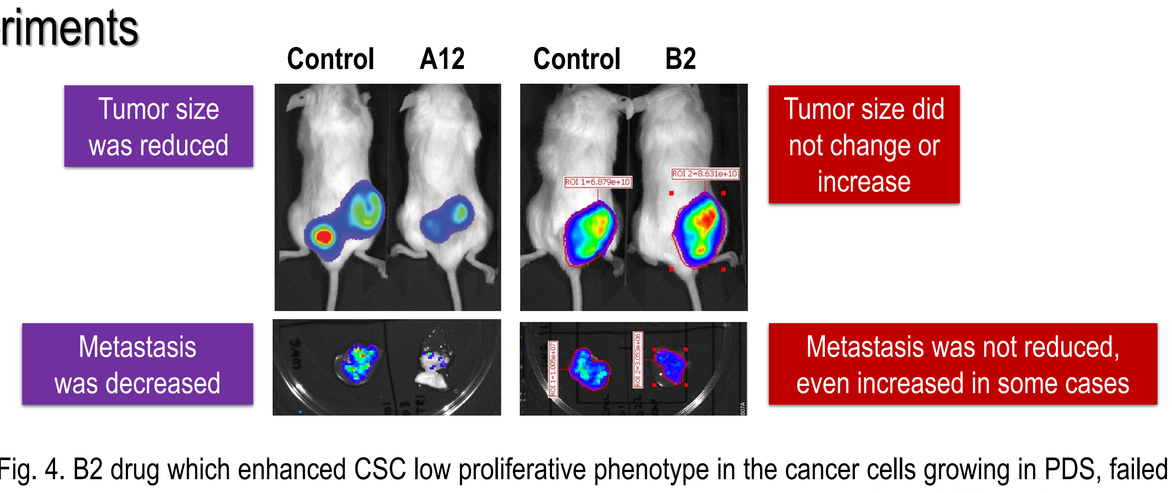


Fig. 4. B2 drug which enhanced CSC low proliferative phenotype in the cancer cells growing in PDS, failed in *in vivo* experiments, even promoting metastasis and increasing tumor size. MDA-MB-231 luciferase tagged cells were injected into mice at a concentration of 0.2×10^6 cells, per injection site. A12 and B2 drugs were administered to mice as 2, 1 or 0.5 mg oral gavage three times a week at a volume of 50 µL.

PDSs induce expression changes of immunotargets, influence T cells killing ability and the response to checkpoints inhibitors therapies.

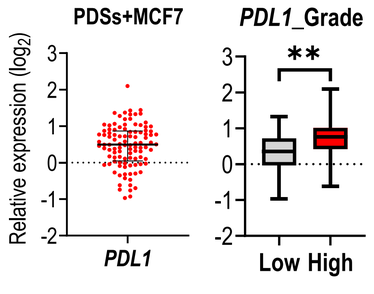


Fig. 5. A) *PDL1* gene expression from 110 breast cancer PDSs cultured with MCF7 cells (individual PDSs represented by dots). B) PDSs generated from high grade tumors induced high expression of *PDL1* gene in PDS cultures.

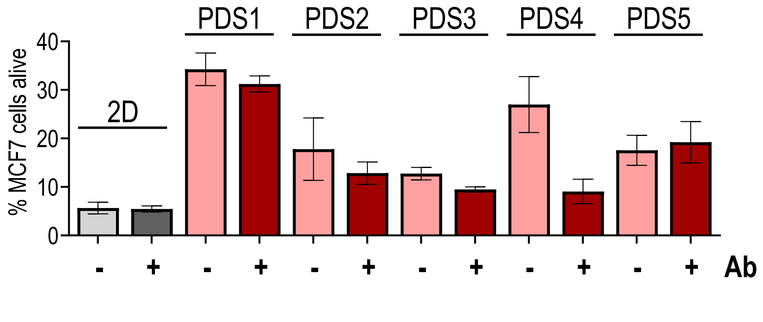


Fig. 6. Viable cancer cells after incubation with activated T cells in 2D and PDSs cultures, with or without addition of checkpoint inhibitor antibody (Ab).

Conclusion

Our findings indicate that the patient-derived scaffold (PDS) is a better representative model for an *in vivo* situation than methods based on standard 2D cell culture and importantly, reveals unique information about the malignancy-inducing properties and immune response modulation of specific TME. PDS model provides a potential complementary diagnosis tool, and a platform for preclinical drug testing and development of personalized therapies.

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