

Project Title: Understanding the role of ECM stiffness in breast cancer progression and nanotherapeutic efficacy through 3D cell cultures.

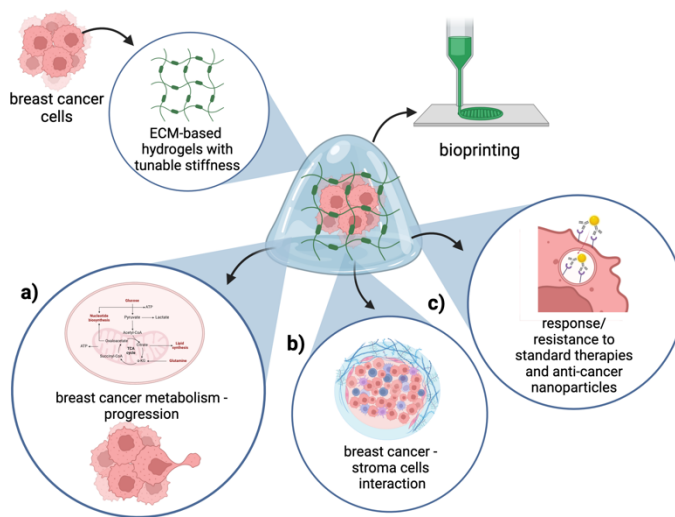
PI: Nora Bloise

Laboratory: “Cells and biomaterials interactions: nanotechnology”, Unit of Biochemistry of Department of Molecular Medicine.

Background: Breast cancer (BC) is a major public health problem due to its high incidence and mortality, being the most common cancer in women worldwide (1). A better understanding of the role of the tumour microenvironment (TME) is essential to improve both its diagnosis and treatment. Extracellular matrix (ECM) stiffness is recognised as a critical factor of the TME, capable of promoting cancer progression by acting as an activator and/or inactivator of specific transcription factors in cancer and stromal cells (2). To facilitate the goal of improving cancer outcomes, new technologies, methodologies, and approaches to better understand cancer are urgently needed. In this context, 3D cell cultures offer a great opportunity to better recapitulate some of the biological, molecular and biophysical features (such as ECM stiffness) of tumours *in vivo*, including physiologically relevant cell-cell and cell-ECM interactions, through appropriate design of matrix cues and dimensionality (3).

Aim: This PhD project aims to develop and characterise tunable 3D engineered cancer models to recapitulate tumour stiffness *in vitro*. The developed 3D engineered models will be used to assess the role of ECM stiffness in **a)** metabolic reprogramming and BC progression, **b)** interaction of BC cells with stromal cells and **c)** response/resistance to standard therapies and anti-cancer nanoparticles. Physiological and tumorigenic media will be used to mimic changes in extracellular pH and cancer dynamic environment will be simulated (e.g., using microfluidic approaches).

The successful development of this project will help to identify molecular networks and the metabolic changes involved in BC progression correlated with ECM stiffness properties.



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Techniques: The project envisages the use of human cancer cell cultures (2D and 3D - ECM-based hydrogels, suitable also for bioprinting-) biochemical (electrophoresis, western/dot blotting, ELISA assays) and molecular approaches (RT-PCR, qPCR), physicochemical characterization techniques, proteomic analysis, cytofluorimetric analysis, Seahorse technology to assess cell metabolism, microscopy techniques (Scanning electron microscopy (SEM), Transmission electron microscopy (TEM), CryoEM, Confocal laser scanning microscopy (CLSM) and Time lapse).

Bibliography: 1) Bray, F., et al., *Ca-Cancer J. Clin.* 2018, 68 (6), 394– 424. <https://doi.org/10.3322/caac.21492>; 2) Deng, B., et al., *Transl Med* 2022, 20, 540. <https://doi.org/10.1186/s12967-022-03768-y>; 3) Fröhlich, E., *Int. J. Mol. Sci.* 2023, 24, 7116. <https://doi.org/10.3390/ijms24087116>.