NanoInnovation 2024

IMMUNE-MODULABLE BIOLOGICAL ENVIRONMENT (MBE) BIOREACTOR TO RECAPITULATE THE COMPLEXITY OF THE VASCULARIZED BREAST CANCER MICROENVIRONMENT

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Breast cancer (BC) has the most highly heterogeneous tumour microenvironment (TME), in which a plethora of biological partners, cancer, immune cells, and fibroblasts incorporated into the extracellular matrix (ECM) simultaneously orchestrate the progression of cancer and immune escape. Furthermore, the presence of T lymphocytes in the TME, indicating an inflamed phenotype, or their absence, indicating a cold phenotype, correlates with a good or poor prognosis in both BC and other solid tumours. Replicating the intricate complexity of the TME *in vitro* is essential for advancing our understanding of the biological mechanisms underlying tumour progression and testing novel therapeutic strategies. For this purpose, a spectrum of *in vitro* models has been developed, ranging from conventional two-dimensional cultures to more sophisticated three-dimensional cultures and tumour-on-a-chip systems. However, each of these models has critical limitations, such as the lack of vascularisation and the absence of an integrated circulating immune system.
In the present study, the objective was to design and produce a bioreactor capable of recapitulating a complex and modulable biological environment (MBE) to emulate perfusable vascularised BC-TME, in a functional relationship with the circulating immune system. Moreover, the extravasation of $CD8^+$ T lymphocytes was enhanced using a nanoparticle-based functionalisation approach and an external magnetic field, to convert the BC cold phenotype into an inflamed one. In the field of predictive and personalised medicine, adopting a more physiological and accurate model, based on the patient's specific immune response within their TME, could provide new insights into BC biology and serve as a platform for testing novel drugs. From this perspective, the MBE, combined with breast cancer organoids, iPSC-derived endothelial cells, and a draining immune system, could represent a significant advancement in the high-fidelity modelling of the dynamic and pathophysiological microenvironment of breast cancer.