Inquire the tumor microenvironment through *in vitro* 3d models with integrated sensing tools

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The tumour microenvironment (TME) defines the complex and dynamic components, cellular and non- cellular, that interact with cancer cells within a tumour. In their native environment, cancer cells are surrounded by stromal cells, the non-cancerous cell components of the TME, which includes cancer- associated fibroblast (CAFs), myofibroblast and various immune cells. This plethora of cells is embedded and structurally supported by the extracellular matrix (ECM), a network of proteins and carbohydrates, such as collagen, glycoproteins, and hyaluronic acid. The alteration or remodelling of the ECM is crucial for tumour cell behaviour, invasion and metastasis developing. Thus, the whole TME plays an important role in cancer progression and response to therapy.

Therefore, there is the crescent urgency to switch from traditional bi-dimensional cell cultures to three- dimensional *in vitro* models that better mimic the complexity of the *in vivo* environment, for understanding the intricacies of the TME and developing effective cancer therapies.

The development of innovative *in vitro* platforms for the investigation of co-cultures of cancer and stromal cells could be performed combining 3D biocompatible structures, such as electrospun fiber matrices, porous scaffolds, and hydrogels, with optical fluorescent ratiometric sensing tools for measuring, with high spatial and temporal resolution, the concentration of key biological analytes, such as oxygen and pH, within the TME.

The optimization of these 3D sensing platforms is paving the way for personalized medicine approaches, in which patient-derived cells are employed, allowing for individualized drug testing and cancer treatment optimization.