Chemotherapy and novel proton radiotherapy in spatially advanced multicellular models of pancreatic cancer: On the design of platform for enabling low cost animal free preclinical treatment testing

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INTRODUCTION: With a 5-year of only 11 % pancreatic ductal adenocarcinoma (PDAC) is one of the deadliest diseases. This is partly attributed to the tumour's resistance to currently available treatment, resulting from a complex and highly heterogeneous tumour microenvironment (TME). A key challenge in cancer tissue engineering is to mimic the different key features of the TME. In this work we have developed robust PDAC biomimetic models for *in vitro* therapeutic assessment.

EXPERIMENTAL: We have advanced our previously developed 3D polyurethane (PU) based polymeric scaffold PDAC model [1,2] by incorporating biological complexity (multiple cell types: pancreatic cancer, pancreatic activated stellate and endothelial cells) [3], spatial complexity (scaffold compartmentalization) and fluid flow (perfusion). Chemotherapy (with Gemcitabine-GEM) [4] as well as proton therapy were carried out within our models. Imaging of cellular proliferation/spatial organization, apoptosis of the different cell types and ECM secretion was carried out along with assessment of biomarkers linked to chemo-resistance.

RESULTS AND DISCUSSION: For chemotherapy treatment, within our static models, we observed that the dual scaffold showed a higher resistance to GEM in comparison to the single scaffold [4]. Our results highlight that the spatial arrangement of the cells, within a 3D model, affect the response to chemotherapy. For proton therapy treatment, pancreatic cancer was more susceptible to proton beam therapy as opposed to photon therapy, the latter resulting in a higher cell viability and lower expression of apoptotic markers post-treatment. Furthermore, the introduction of dynamic flow affected the cell spatial organization, and biomarker expression involved with EMT, matrix remodeling highlighting the importance of fluid flow in PDAC's evolution and response to chemotherapy.

CONCLUSIONS: Our work highlights the importance of spatio-temporal cellular arrangement and interstitial fluid flow for accurate *in vitro* studies of the chemoradiotherapy resistance for PDAC.

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