Tumor-on-chip model to decipher the effect of nanoparticle-mediated photothermia on tumor microenvironment of pancreatic ductal adenocarcinoma (PDAC)

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Pancreatic Ductal AdenoCarcinoma (PDAC) constitutes ~90% of pancreatic cancer cases and is characterized by poor prognosis partly due to therapy resistance [1]. Most of this resistance is attributed to the extensive fibrotic stroma with enhanced desmoplastic effect within the tumor microenvironment that impedes anticancer drug delivery [2]. Nanoparticle-mediated photothermal therapy (NP-PTT) presents a promising technique for adjuvant cancer treatment, through local heating of malignant cells, matrix denaturation, or T cell recruitment among others [3]. Herein, we implement for the first time the NP-PTT in PDAC tumor-on-chip (ToC) to better understand the effect of these NP-mediated therapies and improve their efficiency as combined therapies (with chemo- or immunotherapies).

Our microfluidic system consists of a central chamber for 3D tumor microenvironment modelling & 2 side chambers – for controlled injection of NPs and medium supply. Since collagen I is the most abundant protein in tumor microenvironment [3], we first studied diffusion, temperature increase, and degradation of the collagen matrix alone submitted to NP-PTT. Next, to mimic PDAC microenvironment, we cultured human PDAC cells (PANC-1) in collagen I matrix. NP-PTT treatment conditions combine: iron oxide magnetite NPs coated with PO-PEG-NH_2, 20min exposure to 808nm laser, 1-2W/cm^2 laser power density. The effect of NP-mediated PPT is assessed with confocal microscopy (live/dead assay) for cancer cells and second harmonic generation microscopy (SHG) for the matrix response.

We observed successful on-chip NPs diffusion in collagen I matrix with subsequent temperature increase (37-55°C) through PTT. Using SHG, we showed that collagen I matrix in the chip, in the exposure conditions starts to degrade above 51°C, as also reported previously [4]. Next, we successfully developed a PDAC tumor-on-chip model with formation of tumor spheroids (~100µm) from single pancreatic tumor cells (PANC-1) in collagen, exhibiting invasive phenotype after 7 days of culture (**Figure 1**). This indicates progressive tumor formation and its invasion of the collagen matrix, closely mimicking the *in vivo* conditions. PDAC-on-chip exposure to NP-PTT showed increasing tumor cell death with increasing temperature as a result of the treatment.

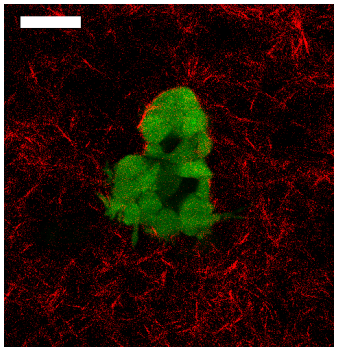

Figure 1: SHG image of PANC-1 cell culture (green) on chip in collagen I (red,6mg/mL), day 7.

With successfully implemented NP-PTT in PDAC-on-chip model, we showed that by tuning NP concentration and/or the heating protocol, ToC device can be finely controlled to promote matrix denaturation and cell death. Our next steps will consist in advancing our PDAC-on-chip model via co-culture of PANC-1 cells with stellate cells to induce the key desmoplastic reaction present *in vivo*. We will thus investigate the matrix remodeling and its effect on NP uptake, heating-induced cell death & matrix degradation to fully study the effect of PTT on PDAC microenvironment and its possible applications for synergized cancer therapies.

References

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