Microfluidics-based 3D Microtumours (3D-MMT) for the Evaluation of Precision Therapies

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Tissue engineering offers considerable promise for the development of disease models for drug evaluation. Over the last two decades, three-dimensional (3D) cell cultures have emerged as effective tissue models, better approximating physiological conditions and bridging the gap between two-dimensional monolayer cultures and *in vivo* models. 3D biomimetic models can mimic complex yet relevant pathophysiological disease mechanisms such as development of tumorigenicity, cancer invasion, and cancer drug response. They can also replicate the heterogeneity and multicellularity of the tumour stromal environment of *in vivo* tumours. The development of precision therapies specifically tailored to tumour models derived from patient biopsies may revolutionize cancer treatment. *In vitro* 3D tumour models complement animal models, as 3D human tumour models may have greater predictive capability over animal models that often exhibit species-dependent drug responses. They could therefore reduce the economic and ethical costs of drug discovery. Here, we report a microfluidic technique for the highly-scalable and reproducible production of microtumours that will be readily translatable for the development of precision therapies.

Multicellular tumour spheroids are a useful model for deciphering the altered response of tumour cells to chemotherapy. However, spheroids produced by current methods often lack sufficient extracellular matrix (ECM), size reproducibility, and typically require at least a week of growth to achieve diameters >500 µm. In many cases they may therefore not recapitulate the role played by the hypoxic core (in the case of spheroids <400 µm), as well as the contribution of cell-cell, cell-ECM interactions to chemoresistance.

To tackle the challenges of spheroid size reproducibility and production time efficiency, we report a microfluidic system[1,2] to fabricate monodisperse, ECM-containing 3D microtumours (diameter: 150 µm to 1000 µm) with high throughput (thousands of highly reproducible microtumours can be produced in 2 hours). This novel microfluidic system can use softer ECM gels such as collagen and Matrigel to produce uniform sized structures. The central aim of this study is to use our microfluidic system to fabricate highly uniform 3D-microtumours (3D-MMT) from patient biopsy-derived cells to evaluate precision cancer therapies. Genomic profiles of *in vitro* microtumours are going to be compared with primary tumour cells to evaluate the recapitulation of heterogeneity by our technique in vitro. A *tumour biobank* is to be established based on this study.

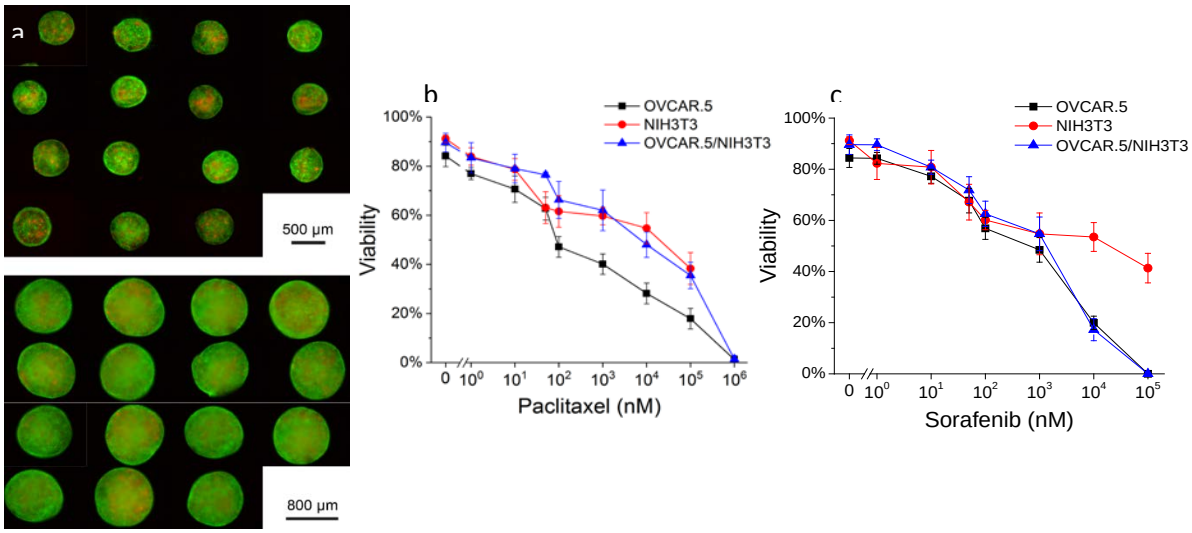

Figure 1. a) NIH3T3/GFP and OVCAR/RFP co-culture 3D-MMT of different sizes in Matrigel at 1.5×10^7 cells/mL. The average diameters are 500 μm, 800 μm. Dose-response curve of viability of 3D-MMT to different drug concentration- b) Paclitaxel targeting the microtubule and c) multi kinase receptor inhibitor, Sorafenib.

References:

[1] S. Ma, et al., Gel Microrods for 3D Tissue Printing, Advanced Biosystems, 2017, 1700075.

[2] S. Ma, N. Mukherjee, Microfluidics Fabrication of Soft Microtissues and Bottom-Up Assembly, Advanced Biosystems, 2018, 1800119.