

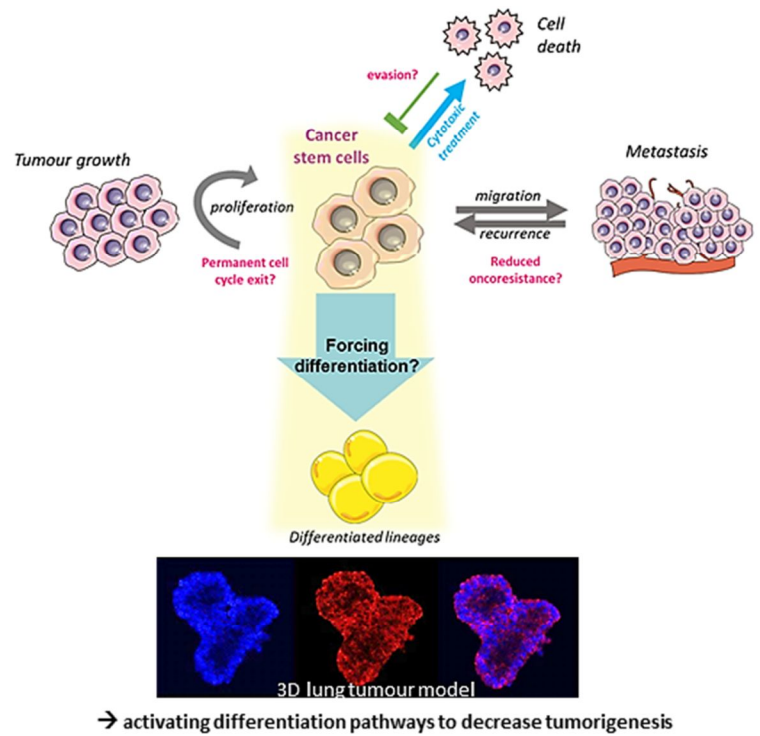
Developing cancer stem cell differentiation models using 3D organoids to potentiate oncotherapies

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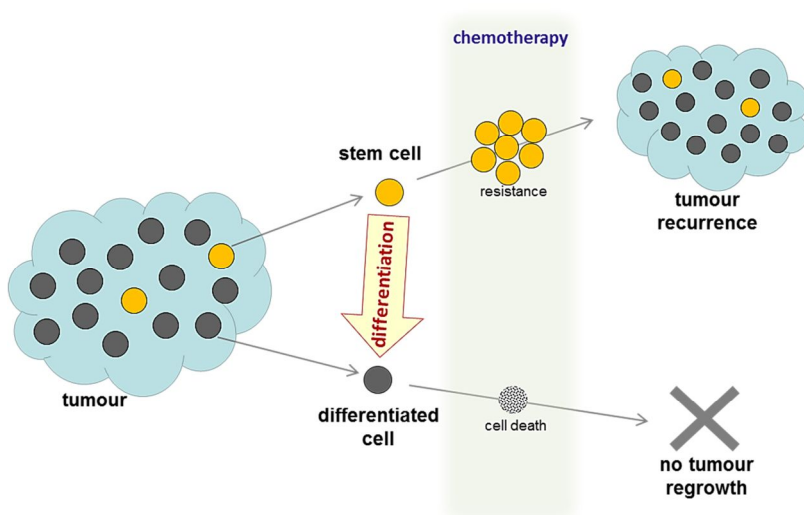
Research Theme/Topic: Cellular and molecular regulation of stem cells & cancer

Background:

Cancer growth and recurrence is linked to the ability of a small population of stem cells within the tumour able to evade oncotherapies, so they can regrow new tumours after the period of chemotherapy. These cancer stem cells (CSCs) represent a key therapeutic target to reduce cancer recurrence and improve the efficacy of existing treatments. Since undifferentiated cancer stem cells are notoriously resistant to standard antiproliferative and cytotoxic drugs used in chemotreatments, one alternative approach to eliminate them is to induce their differentiation towards more differentiated cell types, which are typically more sensitive to oncotherapies and are less pathogenic.



The aim of this PhD project is to develop targeted treatments using an in vitro tumour model, through the production of 3D tumour organoids able to recapitulate the process of tumorigenesis, in 5 experimental steps: (1) Starting from human cancer cell populations (from 2 prominent cancer models: lung and breast cancer), 3D tumour models will be cultured and treated with molecules inducing differentiation pathways. (2) The appearance of differentiated cell types within the tumour models will be monitored both by direct imaging (using confocal/light sheet microscopy) of the samples, and validated by marker expression analysis at the protein (immunodetection) and transcript level (qPCR). (3) The number of CSCs within control and treated tumour samples will be measured by flow cytometry, and their stem cell characteristics will be validated using established stemness assays. (4) In parallel, the pathogenic properties of cells present in the control and treated tumours will be analysed by typical cancer assays (eg proliferation assays, clonogenicity, EMT, migration). (5) Finally, the effect of the differentiation induction will be analysed in an ex vivo model of tumour propagation, to assess changes in chemoresistance for differentiation-induced cells, and to measure the treatment effect on recurrence and invasiveness after chemotherapy.



Outcome: The project will provide a new preclinical evaluation of differentiation as an anti-cancer strategy for 2 prominent types of solid cancers. By targeting CSCs within a 3D tumour model rather than in monolayer cultures, the results produced will be more physiologically relevant to the in vivo situation, where CSCs can be shielded from treatments by surrounding tumour cells.

Techniques: Human cancer cell cultures, 3D organoid production, disease modelling, stem cell marker detection, differentiation induction, confocal/light-sheet imaging & 3D reconstruction, clonogenic & migration assays, transcriptome analysis, flow cytometry & cell sorting.