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# TARGETING CRC-SC FOR DIFFERENTIATION – A 3D SCREENING SYSTEM FOR DIFFERENTIATION THERAPIES

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Cancer stem-like cells (CSC) are a subpopulation of tumour cells with the extraordinary characteristic of self-renewal and also can replenish themselves. The emerging concept of differentiation therapy advocates that the efficacy of conventional anticancer treatment will increase upon forced differentiation of CSCs. Therefore, follow-up discovery of new drugs will involve selective CSC targeting and allowing them to descend to bulk cancer cells will make them easily targeted by conventional treatment. Currently, there is no known compound(s) that drive colorectal cancer (CRC)-SC differentiation. Moreover, current *in vitro* models fail to comprise tumour heterogeneity and predictive patient outcome in preclinical setting. We attempt to harness a patient relevant *in vitro* screening system to identify small molecule(s) and to cross-examine CRC-SC differentiation. At present, we have identified 4 candidate drugs that have been screened from a library of small molecules consisting of 707 compounds for their differentiation induction potential. For this, we have established a novel methodology to screen small molecule-based drugs targeting 'stemness' properties on live 3D colonospheres derived from CRC cell lines. We have optimized our pilot screening with a clinically relevant HDAC inhibitor and a fluorescent rosamine dye CDy1 in a high throughput plate reader screening (PRS) manner to detect reductions in fluorescence staining on live 3D colonosphere. Our results suggest that compounds that induce differentiation can be identified based on the reduction of CDy1 intensity in 3D colonospheres, backed by immunostaining of stemness and differentiation markers.Our initial screening suggest that 6% of the total compounds might be involved in inducing differentiation in CRC-SC obtained from three CRC cell lines. These compounds were identified based on distinct morphology changes, colonosphere sizes and intensity of CDy1. Further follow up data suggest that three of these compounds antagonize nuclear β-catenin, known to regulate self-renewal at adenoma and carcinoma stages. We have selected 4 compounds based on their ability to suppress colony formation, cell growth, and preliminary effects shown for beta catenin expression. Upon finishing this screening on 3D colonosphere representing CSCs, we have been focusing on identifying the mechanisms of our candidate drugs and how they regulate differentiation on CRC-SC. Using proteomic approach and biochemical analysis, we're currently looking at specific targets for these drugs and to elucidate their mechanisms. Simultaneously, we are also evaluating these drugs on patient derived organoids and tissue explants obtained from both tumour and normal adjacent tissue to investigate drug specificity on CSC vs NSC. The lack of relevant models and suitable screening methodology are two major impediments in CRC drug discovery. This study demonstrates the application of colonospheres in drug screening and could potently characterise the mechanisms involved with defined compounds in CSCs eradication, a major aspect behind cancer recurrence, resistance and mortality. Our studies are underway to identify the targets of candidate drugs and exploring their mechanism on CRC-SC specificity. This would be relevant to decipher the differentiation induction pathways in CRC-SC.

## BIOGRAPHY

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