Principal Investigator: Prof Jeremy Turnbull

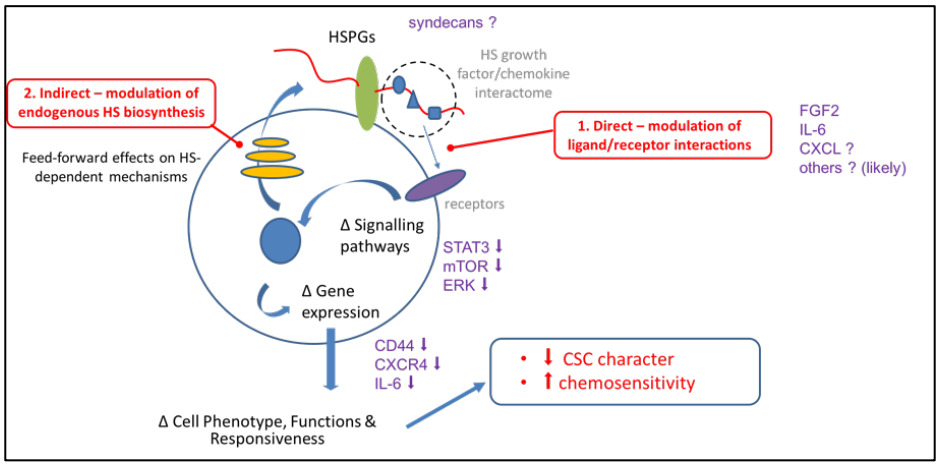
Grant Title: Dissecting mechanisms underlying regulation of cancer stem cells by Heparan Sulfate

Cancer stem cells are emerging as a key new target for anti-cancer therapeutics, whereby reducing their numbers or altering their phenotype could greatly enhance the efficacy of existing treatments. We have discovered that heparin and heparan sulfate (HS) can cause phenotypic switching of breast cancer stem cells away from aggressive tumorigenic behaviour, and also render them more sensitive to chemotherapy agents. Furthermore, we have preliminary evidence for the underlying mechanisms of action of heparin/HS via multiple mechanisms affecting cell signaling and apoptotic pathways.

Objective: to dissect the mechanisms of action of HS in phenotypic switching and chemotherapeutic sensitization of cancer stem cells (CSCs).

Methods: breast cancer cell line culture; fluorescence activated cell sorting and analysis; qRT-PCR; Western blotting; phosphoprotein ELISA slide assays; modified heparins.

Results: We have established that exogenous HS or heparin alter multiple signaling pathways, resulting in enhanced apoptosis in CSCs. This provides a mechanism for reduction of the CSC sub-populations in breast cancer cell lines. We also demonstrated differential effects of selectively modified (non-anticoagulant) heparins on CSC phenotype and chemosensitivity, which open up potential for novel non-anticoagulant heparins to be used as a therapeutic basis for pharmacologic targeting of breast CSCs, to enhance chemotherapeutic regimes.



Working model: HS modulates BC stem cell phenotype via modulation of multiple signalling pathways

Discussion: Our overall results have revealed important new information which inform the development of novel heparin-based regulators of cancer stem cell phenotype and chemosensitivity, opening up new opportunities for pharmacological treatments for cancer.