

## **Cancer stem cells: the reservoir for growth and resistance in malignancies**

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Observations going back almost half a century have demonstrated that tumours are highly inefficient at generating clonal growth in both *in vitro* and *in vivo* assays. As an explanation for this it has been proposed that all tumour cells have the potential for self-renewal and proliferation, but that the probability of this is low. An alternative proposal is that only a small proportion of tumour cells actually contain the ability to regenerate and propagate the tumour, the so-called “cancer stem cell”. Recent advances in isolation of discreet cellular populations and *in vivo* tumour regeneration assays have demonstrated the existence of this cancer stem cell population for many malignancies. Cancer stem cells were first demonstrated for human acute myeloid leukaemia, and have been subsequently described in human breast cancer and CNS tumours and in murine tumours.

Current treatment regimens for malignant disease usually demonstrate some initial efficacy in tumour bulk reduction. However, the vast majority of tumours still recur or metastasise, often with new mutations which confer resistance to therapy. A likely explanation for this is that current treatments preferentially spare the cancer stem cell compartment, allowing it to form a reservoir for recurrence, metastasis and resistance. An illustrative example is chronic myeloid leukaemia (CML), where the causative BCR-ABL mutation occurs within the normal CD34+ stem cell. A population of quiescent CD34+ BCR-ABL + CML stem cells have been demonstrated which are primarily resistant to the selective targeted ABL kinase inhibitor Glivec, while CD34- BCR-ABL cells remain exquisitely sensitive. This CD34+ population has also been shown to contain point mutations which confer secondary resistance to Glivec and further karyotypic abnormalities which facilitate progression to the acute leukaemia phase of the disease.

The biology of the cancer stem cell is poorly understood. As it is the critical target for the treatment of malignant disease, it seems likely that a greater understanding of its biology would lead to an improvement in cancer therapeutics. Therefore the molecular and cellular characterisation of cancer stem cell populations must be a priority in cancer biology. Ongoing research examining self-renewal pathways and targeting apoptotic pathways in leukaemia will be discussed as illustrative examples. It is hoped that a greater knowledge of the biology of cancer stem cells and how this differs from normal stem cell biology will allow for selective targeting of cancer stem cells without collateral damage to normal stem cells, facilitating improved results in the treatment of many cancers.