Supplementary Information S2 | The cancer stem cell hypothesis

The discovery of cancer stem cells (CSCs) emerged from a deeper understanding of normal tissue biology. The generation of a complete and functional tissue is a complex and highly regulated process. Furthermore, most tissues continue to have cell turnover throughout life through a series of proliferation, differentiation and cell death events. In many tissues, homeostasis is regulated by a hierarchy of cell types, with stem cells sitting at the apex of the process. By definition, the stem cell must be capable of both continuous self-renewal as well as the ability to generate progenitor cells with limited replication competency but the full diversity of differentiation potential to reconstitute all the cell types of a specific tissue.

For several years, it has been argued that multiple types of cancers use a highly analogous hierarchy. The majority of primary tumor cells, for example from breast and prostate cancers, are not able to re-constitute a full tumor and have limited replication potential in isolation. Therefore, to propagate primary tumors *in vivo* thousands of cells from crude tumor isolates must be transplanted. This led to the model that, within these crude transplants, there reside rare cells that uniquely maintain the stem-like properties of full tumor reconstitution with complete cellular diversity[1]. A combination of fluorescence activated cell sorting (FACS) and limiting dilution studies in several tumor types has lead to significant refinements of the identity of CSCs and facilitates their study under highly purified conditions. In the end, successful treatment of cancer must include targeting of CSCs and, therefore, the importance of understanding how our current and developing therapies impact this population cannot be overstated.

Reference

1. Reya, T., Morrison, S.J., Clarke, M.F. & Weissman, I.L. Stem cells, cancer, and cancer stem cells. *Nature* **414**, 105-11 (2001).