Difference in susceptibility towards chemical compounds of glioblastomas stem cells in the proliferative or quiescent state

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Glioblastomas are highly aggressive brain tumors without available curative treatment. Cancer cells with stem cell properties have been isolated from these tumors and have been proposed to be responsible of tumor growth and of traditional chemotherapy and radiotherapy resistance. These cells known as cancer stem cells (CSC) and representing a fraction of the whole tumor, are able to self-renew and differentiate to recapitulate the phenotype of the parental tumor. Thus a new paradigm in cancer therapy prones the targeting of CSC.

Our study aims to find new molecules able to interfere with the growth of stem cells isolated from human glioblastomas and to decipher their mechanisms of action. TG01 cells isolated from Malignant Glio-Neuronal Tumors (MGNT) are studied in our laboratory. These cells are able to be either in a proliferative state or in a non-proliferative state called quiescence. Quiescent cells have distinct physiological characteristics compared to proliferating cells and may respond differently to chemical compounds. Assessing the difference in response to chemical compounds is an important step in the understanding of the physiopathology of these cancer stem cells and the identification of more efficient treatments of glioblastomas. We used a viability cell-based assay for high throughput screening of chemical libraries to assess the effect of 1120 chemical compounds on proliferating and on quiescent TG01 cells. Hits were validated by establishing dose/response curves. Confirmed hits include 6 molecules more active on proliferating cells, 6 molecules more active on quiescent TG01 cells whereas 12 molecules were active on both proliferating and quiescent cells. Active molecules were classified based on their known therapeutical activity. Reappraisal of the pharmacological effects of the compounds will be therefore discussed.

Reya *et al.* Stem Cells, Cancer, and Cancer Stem Cells (Nature (2001) 414, 105-111).
Singh *et al.* Identification of a Cancer Stem Cell in Human Brain Tumors (Cancer Research (2003) 63, 5821–5828).
Patru et al. CD133, CD15/SSEA-1, CD34 or side populations do not resume tumor-initiating properties of long-term cultured cancer stem cells from human malignant glio-neuronal tumors (BMC Cancer 2010, 10:66).