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**Targeting Glioblastoma stem cell plasticity : toward an innovative and efficient anti-cancer stem cell therapy**

Glioblastomas (GBM) are lethal primitive brain tumours characterized by a strong intra-tumour heterogeneity. Besides various genomic abnormalities or epigenetic features that exist among the tumor cells, a sublevel of complexity, resides in the co-existence of populations of cells functionally divergent (tumorigenic or not, mitotic or not, resistant to treatment or not) and represented in variable proportions within tumors while sharing similar genomic abnormalities. Such a functional heterogeneity is mainly due to GBM cell plasticity that allows the inter-conversion between a stem-like (glioma stem cells (GSC)) or a more differentiated phenotype. Such tumor cell plasticity plays prominent contribution in tumor progression and the response to conventional treatment, principally by favoring a stem-like state. Face to this observation, it is becoming obvious that targeting stem-like properties of tumor cells is a prerequisite for improving anti-cancer therapies, and to this aim our paradigm is to develop a differentiating strategy to fight against the stem-like phenotype of tumor cells. In collaboration with Dr Maria Duca (ICN, Nice) we have identified and developed a novel molecule (DVXXX, patent deposited number EP19306237.9) capable of repressing GSC stem-like properties including clonal amplification. This compound is highly efficient in vivo and more than 80% of the treated mice did not develop any tumors following orthotopic xenografts of patient-derived GSC. In addition, this compound strongly increased GSC sensitivity to TMZ providing interest for combined treatment in first and second line of therapies. The compound is not toxic (XTT and trypan blue staining) for normal cells such as kidney, normal neural stem cells and human hepatocytes, not toxic for mice after months of treatment. DVXXX mode of action relies on the blockade of NANOG (essential for GSC maintenance) translocation in the nucleus by directly targeting KPNB1, a nuclear transporter, thus providing a specificity of action restricted to GSC.