Oncolytic Herpes Simplex Virus type 1 armed with CXCL12-antagonist "P2G" to impair glioblastoma stem-like cells self-renewal and migration

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Glioblastoma is an aggressive high-grade astrocytoma. Current standard treatments consist of maximal surgical resection followed by chemo-/radio- therapy. Unfortunately, this treatment protocol is impaired by incomplete resections and systematic relapses often leading to poor prognoses. Migration of CXCR4+ glioblastoma stem-like cells (GSCs) from the tumor mass to the sub-ventricular zone (SVZ), following a CXCL12 gradient, participates to the disease progression. When hidden in the SVZ niche, GSCs evade resection and become resistant to radio-/chemo- therapy. High expression of CXCR4 positively correlates with tumor progression, recurrence, and low patient survival. Thus, GSCs and CXCL12/CXCR4 pathway appear as interesting targets for new therapies against glioblastoma growth, invasion of brain tissues and recurrence.

In this context, we have developed an attenuated oncolytic HSV-1 (oHSV) expressing a specific CXCL12/CXCR4 pathway inhibitor (oHSV-P2G) that leads to a continuous production of the inhibitor at the tumor site. oHSV-P2G is expected to cause tumor cell lysis and to disrupt CXCL12/CXCR4 pathway, thereby interfering with GSCs self-renewal ability and preventing their migration towards the SVZ. This could facilitate maximal resection, reduce tumor size and probability of relapse, and increase overall survival.

Our results showed that *in vitro*, neural stem markers expression, self-renewal and migration abilities of both murine and human GSCs are impaired upon treatment. Moreover, in an *in vivo* orthotopic immunodeficient mice model, tumor cells migration towards the SVZ was shown to be reduced. Future experiments will focus on combined treatments in which oHSV-P2G will be administered with chemo-/radio- therapy to show potential sensitization of radioresistant GSCs.