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## IL12 secreting retargeted fully virulent herpes simplex virus as therapy for high grade glioma

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High Grade Gliomas (HGG) are the main malignant tumors of central nervous system and, so far, almost incurable because of the radio- and chemo-resistance. A novel therapeutic approach, based on recombinant oncolytic Herpes Simplex Viruses (oHSV) that target cells expressing specific receptors, combined with immunomodulation, fits in the field of new promising strategies aimed at enhancing a targeted and efficient therapeutic response. We evaluated the effects of a retargeted fully virulent HSV-1 (named R-115) armed with mIL12 on established syngeneic hHER2 expressing HGG. R-115 exhibited a specific hHER2 tropism. When locally injected in large established gliomas, it is effective in counteract tumor growth, doubling the median survival after treatment and we observe for the first time the appearance of long survivors associated with the development of the resistance to recurrence of the same neoplasia. Retargeted viruses are intrinsically safer than attenuated ones and unlike other studies, we obtained a substantial percentage of long survivors after a single injection of viral preparation into fully established gliomas that could potentially improve with earlier or repeated treatments. Moreover, we pointed out that mIL12 expressing R-115 enhanced the production of antibodies targeting transplanted glioma cells and it makes the tumor tissue accessible to infiltration of T-lymphocytes. Results obtained represent a step forward towards the possibility to treat HGGs with retargeted oHSV.

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