

## EDITORIAL

## Emerging Concepts and Therapeutics Strategies for the Treatment of Brain Tumors

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“There is no satisfactory treatment of glioblastoma multiforme of the brain” was the introductory sentence of an article published in 1967 by Jelsma & Bucy [1]. Unfortunately this poor prognosis has not changed during the last 45 years and this pessimistic statement remains largely valid. At that time the 5 years survival was less than 10%. A historical comparison of Kaplan-Meier survival plots made in 2000 by Dr. Eric Holland showed that about 90% of patients died within 5 years. Due to the poor prognosis of patients GBM has been called “the Terminator” [2]. Since its introduction in 2005, temozolomide (TMZ) has become the standard treatment despite the fact that the 5 years survival rate modestly increased around 20% [3]. As in 2010, TMZ in selected groups of patients had limited benefit [4]. Kast *et al.*, pointed out that the 22 clinical trials reported in 2012 using drugs that showed promising potential in preclinical studies were found to minimally improve quality of life and overall survival when compared to the “Stupp protocol” [5].

In this hot topic issue we highlight few exciting areas that may provide useful ways to understand the complexity of glioma biology and its implication for the development of novel effective therapeutic strategies. Like in other cancers, the isolation of putative cancer stem cells (GSCs) in glioma cell lines and fresh specimens were received with great enthusiasm. The review by Alexandru *et al.* “Selective Therapeutic Targeting of Malignant Glioma Stem Cells” [6] discusses the current therapeutic modalities for glioma treatment and highlights the potential underlying mechanism(s) for resistance to radiation and TMZ attributed to the presence of GSCs. Later on, the authors provide a list of potential targets that could be exploited to overcome the inherent resistance of GSCs. The list included microenvironmental factors (hypoxia), signaling pathways (Notch, Hedgehog – GLI, Epidermal growth factor receptor (EGFR), transforming growth factor beta (TGFβ), platelet derived growth factor receptor (PDGFR)), the c-Myc oncogene, the Bmi1 epigenetic silencer gene, overexpression of chemokine receptors, adhesion molecules, bone morphogenic protein (BMP), the stem cell marker CD133, miRNA and potential targets to overcome GSC immune surveillance escape. Some of these promising targets are further discussed in other articles in this hot topic issue. The article “Microenvironment and Brain Tumor Stem Cell Maintenance: Impact of the Niche” by Herold-Mende and Mock [7] gradually expands our understanding of the complexity of gliomas and provides additional therapeutic targets: the interactions with stromal cells, immune cells, their adjacent endothelial cells and the extracellular matrix.

Immune targeting therapies are also likely to benefit from a better understanding of glioma biology related to cancer stemness. It was recently found that the cancer stem cell subtype classified as CD133<sup>+</sup> CSCs (proneural-like CSCs) or CD133<sup>−</sup> CSCs (mesenchymal-like CSCs) may determine the response to immunotherapy and survival [8]. The original research article “Tapasin and human leukocyte class I dysregulation correlates with survival in glioblastoma multiforme” by Thuring *et al.*, adds additional support correlating the dysregulation of tapasin and human leukocyte class I with survival of patients with GBM [9]. The influence of HLA-2 antigen presentation and tapasin is discussed in detail in the review by Darabi *et al.*, “HLA-I antigen presentation and tapasin influence immune responses against malignant brain tumors – considerations for successful immunotherapy”, that brings discussion on IFNγ therapy, cytostatics and irradiation [10].

Successful treatment of gliomas would likely require multimodality treatments and thus a better integrated knowledge of glioma biology is essential. The article “Translational gap in glioma research” by Ma *et al.* [11] raises awareness of the poor success on translating basic research into clinical trials. The potential of local delivery and nanodrugs-based therapies as way to increase the effectiveness of anticancer drugs and overcome the blood brain barriers is reviewed in the article “Overcoming the blood-brain barrier for chemotherapy: limitations, challenges and rising problems” by Wang *et al.* [12].

Due to the heterogeneity and complexity of glioma tumors prolonged treatment with high doses of anticancer agents will be necessary to cure cancer. Indeed few attempts has been done recently in this direction: i) a recent study showed that prolonged administration of adjuvant temozolomide improved the survival in adult patients with glioblastoma [13], ii) a two phase treatment using prolonged high exposure to anticancer drugs (e.g. alkylating agents or DNA replication inhibitors) followed by prolonged exposure to low concentration of salinomycin has been shown *in vitro* to prevent regrowth of glioma surviving cells [14, 15]. iii) a new proposal to increase overall survival and quality of life include adding already-marketed growth factor-inhibiting drugs to low dose continuous temozolomide [5].

Future improvements in drug delivery either by local or nanoparticles-based therapies in combination with prolonged treatments with less toxic drugs will be important to overcome the challenges due to tumor heterogeneity and the presence of the blood brain barrier. The potential tumorigenic properties of all glioma cancer cells likely due to their plasticity properties and its modulation by the microenvironment that allow interconversion between glioma stem cells and non-glioma stem cells [16-19] is a novel concept that is gradually being accepted as one of the major challenge to completely eradicate the tumor and prevent tumor relapse. The concept that to cure gliomas all cancer cells should be eliminated at once [16, 20] is now replacing the classical belief that cancer stem cells should be the main therapeutic target. For instance Schonberg *et al.* recently stated “To achieve a brain cancer cure, all tumor cells, particularly the brain cancer stem cells, must be eliminated” [21].

To be successful, other types of therapies not discussed in this hot topic issue but actively investigated (e.g. gene therapy, boron neutron capture therapy) should also take in consideration these novel concepts of glioma biology. At present nobody can predict which type of therapy will be the effective one and therefore any promising strategy is worth pursuing. However, as our knowledge of the complexity of gliomas increases it is likely that a multidisciplinary approach will be more advantageous over a single monotherapy modality. Novel multidisciplinary strategies need to be explored at earlier stages (during the preclinical development) and integrated during early clinical trials

to avoid the translational gap of glioma research that if not corrected the prognosis of patients will remain as poor as it has been for the last five decades.

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