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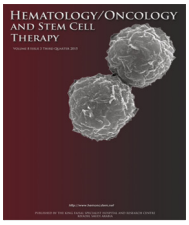

REVIEW ARTICLE

# Current status and challenges of stem cell-based therapy for the treatment of glioblastoma multiforme

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**Abstract**
Glioblastoma (GB) is one of the most malignant types of central nervous system tumours, classified as grade IV by the World Health Organization. Despite the therapeutic advances, the prognosis is ominous, with a median survival of about 12–15 months post diagnosis. Although therapeutic options available can increase the survival, they are ineffective in treating patients with GB. Impairing factors such as the blood–brain barrier, cancer stem cells, and infiltration into brain parenchyma lead to failure of current therapies. Therefore, clinicians need novel/alternative effective strategies to treat GB. Due to their ability to preserve healthy tissues and to provide an effective and long-lasting response, stem cells (SCs) with tropism for tumour cells have attracted considerable attention in the scientific community. As is the case here, SCs can be used to target brain tumour cancer cells, especially high-grade malignant gliomas like GB, by overcoming the resistance and exerting benefits for patients affected with such lethal disease. Herein, we will discuss the research knowledge regarding SC-based therapy for the

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treatment of GB, focalising our attention on SCs and SC-released extracellular vesicles modified to express/load different antitumour payloads, as well as on SCs exploited as a diagnostic tool. Advantages and unresolved issues of anticancer SC-based therapy will also be considered.



**Contents**



## Introduction

According to the 11th version of the International Statistical Classification of Diseases and Related Health Problems by the World Health Organization, glioblastoma multiforme is currently classified as glioblastoma (GB) (02 Neoplasms > Neoplasms of brain or central nervous system > 2A00 Primary neoplasms of brain > 2A00.0 Gliomas of brain > 2A00.00 Glioblastoma of brain). The highly infiltrative nature of glioma into the surrounding normal brain tissues, the high rate of migration from the tumour core, and the ability to generate secondary microsatellite tumours in normal brain parenchyma are the major causes of poor prognosis in patients with GB [1]. Traditional treatments for GB include surgical resection and chemoradiation therapy. However, since the removal of microsatellite tumours by surgery is not feasible, GB remains one of the most fatal forms of malignant primary brain tumours [2,3]. More than 10,000 new cases of GB are diagnosed every year in the United States [4]. The treatment strategies available to clinicians, such as external beam radiation and systemic chemotherapy, have a limited success due to their inability to target specifically disseminated tumours and due to the side effects like toxicity and cognitive impairment potential [5,6]. Treatment for GB is impaired by the presence of the natural brain barrier, that is, the blood–brain barrier [7,8]. The average time to GB recurrence is about 6 months, and the median survival of patients with GB is 12–15 months [9]. Causes of recidivism are complex including no clear tumour margin for complete resection, high proliferative index, resistance to chemotherapy and radiotherapy especially in cancer stem cells (CSCs), and cerebrospinal fluid dissemination. The average CSC count for GB is 3–5% [10]. Usually, CSCs are in a quiescent state but when they are stimulated by surgery, chemotherapy, and radiotherapy, their population may grow exponentially [11]. When CSCs regrow rapidly, patients eventually die of tumour recurrence. Therefore, the targeting of these stem cells (SCs) is a valuable therapeutic option that can increase the survival of patients with GB [10,12]. By contrast, cancer is the result of the uncontrolled migration of SCs [12]. A theory that continues to gain traction is the SC

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theory of cancer, which posits that cancers arise from CSCs present in the tissues and accumulate all the mutations necessary to initiate tumorigenesis [13]. As shown in Fig. 1, there are five methods for eradicating CSCs, including the CSCs of GB. However, to overcome the resistance and benefit the patients affected with such a lethal disease, novel alternative strategies are warranted. The designing of novel drug delivery systems (DDSs) to target GB and relative residual disseminated brain tumours is raising considerable interest. Compared with conventional DDSs, SC-based DDSs include several advantages such as drug delivery efficacy, sustained drug release, extended drug half-life, and limited immunogenicity and cytotoxicity [14]. Besides, in addition to their self-renewal and differentiation capabilities, SCs have antitumour and migratory properties and they do not elicit immune system responses [15]. Thanks to these features, SCs are an eligible candidate to deliver anticancer payloads to high-grade malignant gliomas, especially GB [16].

## Stem cells

### Types

Throughout the lifespan, SCs play a key role in both the generation and regeneration of the tissues in all living organisms including humans [17]. There are four defined types of SCs: two physiological types that are present at different stages of life-embryonic SCs (ESCs) and adult SCs (ASCs);

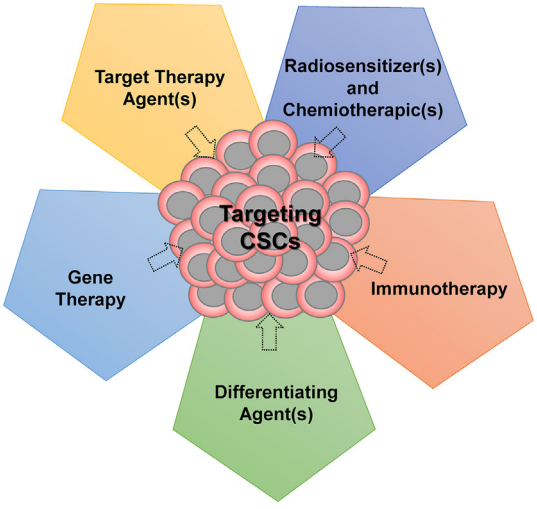


**Fig. 1** Methods currently used to treat cancer stem cells (CSCs), including CSCs of glioblastoma. There are at least five methods used for eradicating CSCs. First method is focused on targeting new molecular protein signal pathway(s) of CSCs with new targeting therapeutic agent(s). Second method is focused on increasing the radiotherapy and chemotherapy sensitivity of CSCs by using reactive agent(s). Third method involves the use of immunotherapy. Fourth method uses differentiation agent(s) to promote the CSCs to differentiate into normal cells. Fifth method involves the use of gene therapy to reduce CSC proliferation.

engineered or ''induced" type (induced pluripotent SCs [iPSCs]); and pathological type (SCs present in cancer (CSCs) [18]. ASCs and iPSCs are more suitable candidates than ESCs for therapeutic purposes [16]. Haematopoietic SCs (HSCs) are well-characterised ASCs. They are present in the bone marrow and can differentiate into all the blood cell types, including myelocytes, lymphocytes, and erythrocytes [19]. iPSCs are derived from genetically engineered skin or blood cells and could be reprogrammed into an embryonic-like pluripotent state, resulting in the development of a plethora of cell types potentially usable for therapeutic purposes [20]. Mesenchymal SCs (MSCs) are spindle-shaped, fibroblast-like multipotent SCs that have the potential to generate different types of tissues, such as the cartilage, bone, muscle, tendon, ligament, and fat [21]. MSCs can be obtained from peripheral blood, bone marrow, placenta, adipose tissue, skin, dental pulp, and umbilical cord blood [22]. However, bone marrow, umbilical cord blood, and adipose tissue are the best sources of MSCs, which are involved in several preclinical studies [23]. Recent findings have shown that MSCs derived from iPSCs exhibit properties similar to MSCs derived from bone marrow and can be used as a promising alternative cell source for MSCs and SC-based therapies [24,25]. Neural SCs (NSCs) are found in the dentate gyrus of the hippocampus and the subventricular zone (SVZ) [26,27], which are the two main neurogenic niches of the adult brain [28]. NSCs are multipotent SCs that can self-renew or differentiate into the three main neural cells-neurons, astrocytes, and oligodendrocytes [29]. NSCs are suitable for SC-based therapy targeting brain tumours [16,30].

### Tumour tropism

Cell migration occurs either during physiological processes, such as the organism development and cell turnover, that during the replacement of damaged tissue, inflammation and cancer progression [31]. Homing capacity has been described in some somatic SCs, but not well known for other tissue residential SCs. The ASCs with the most remarkable migratory capacity are undoubtedly the HSCs [12]. Under physiological conditions, there is a continual flux of HSCs between the blood and bone marrow [32]. Different injuries, such as haemorrhagic shock, inflammation, and stroke lead to a significant increase in the pool of HSCs in circulation [33], although their contribution to tissue repair and regeneration is unknown. During bone marrow transplantation, the remarkable ability of HSCs to migrate and return to the bone marrow niche is harnessed because allogeneic HSCs also exhibit tropism to recipient bone marrow and give rise to all haematopoietic cells [34]. Homing capacity is also well described for MSCs. It is believed that MSCs reside in perivascular niches [35], and their presence in each tissue could facilitate their migration and arrival at injury sites. The endogenous migration of bone marrow-derived MSCs under injury situations has been described. MSCs enter circulation and reach injured tissues to promote tissue regeneration [36]. The feature of MSCs to migrate to the sites of tissue damage and inflammation is pivotal in the SC-mediated GB treatment [37]. Moreover, the migration or homing of administered MSCs in a therapeutic context is

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clearly of great interest due to their potential for regenerative medicine applications [12]. MSCs make therapeutic drugs *in situ*. It is, indeed, the patient's own site- and tissue-specific resident SCs that construct the new tissue as stimulated by the bioactive factors secreted by the exogenously supplied MSCs. Thus, to more accurately reflect the fact that these cells home in on sites of injury or disease and secrete bioactive factors that are immunomodulatory and trophic (regenerative), it has been suggested to change the name of MSCs to Medicinal Signalling Cells [38], maintaining the acronym MSCs. In the healthy adult brain, NSCs residing in the SVZ divide and transit into amplifying cells that consequently differentiate into neuroblasts [26,27]. Several mammalian organs remain in a state of flux throughout life, suggesting a strong activity of their stem and progenitor cell populations. In contrast to ASCs, progenitor cells are more pre-committed to differentiate into a specific cell type, and their self-renewal capacity is limited. Progenitor cells can, therefore, be regarded as an intermediate state between SCs and the fully differentiated cells [39]. In the intestine, epithelial SCs are localised near the bottom of the intestinal crypts and, during the renovation of the epithelia, they proliferate and differentiate into progenitor cells, which mature and migrate until they reach the epithelium [40]. Neural progenitor cells are continuously being produced in the adult brain, but their genesis is confined to the SVZ [26,27]. Following brain damage, neural progenitor cells migrate into the injured region where they attempt differentiation and repair [41]. However, the brain's intrinsic repair mechanisms are largely ineffective, especially in the case of extensive lesions [42].

Studies have emerged showing glioma SCs (GSCs) to represent a subpopulation of cells within GB that possess self-renewal ability and high proliferative capacities, leading to immediate activation of tumour invasion and metastasis [43,44]. Therefore, the treatment of GSCs is vital to prevent tumour recurrence. Normal SCs preferentially migrate towards tumour sites reaching CSCs; thus they can be used to target GSCs in GB therapy. Interactions between normal SCs and GSCs reduce tumour proliferation, angiogenesis, and metastasis, decreasing inflammation and apoptosis too. Human MSCs and HSCs can target GSCs and inhibit the growth of GB [45,46].

The regulation of migratory responses as well as quiescence, proliferation, and differentiation of SCs is governed by signalling from the niche [12]. Extracellular factors prompt cells to migrate towards specific sites of the body [1]. C-X-C chemokine receptor type 4 (CXCR4) and its ligand, stromal-derived factor 1, play an important role in SC migration [31]. Other chemokines involved in SC migration are urokinase-type plasminogen activator receptor (uPAR) [47], platelet-derived growth factor [48], transforming growth factor β receptor 2 [49], macrophage migration inhibitory factor/CXCR4 [50], vascular endothelial growth factor receptor 2 (VEGFR2) [51], and matrix metalloproteinase 1/proteinase-activated receptor 1 [52]. All these chemokines are also involved in SC migration towards the tumour site. Other factors relevant for SC migration and affecting tumour homing include the heterogeneity of the SC population, the culture conditions, as well as the neighbouring tumour microenvironment (e.g., the degree of hypoxia and inflammation, angiogenesis) [16]. The homing property of SCs makes them a potential candidate for the treatment of central nervous system disorders including neoplastic, ischemic, and demyelinating lesions [53].

## Anticancer factors secreted or carried by stem cells

Through their secreted factors or their physical interaction with cancerous cells, SCs exhibit an antineoplastic effect [16,28]. As summarised in Fig. 2, SCs can be modified in various ways or carried with different payloads to improve their anticancer effect against GB.

The tumour microenvironment has progressively been shown to dictate aberrant tissue function and to play a critical role in the subsequent evolution of malignancies [54]. The tumour microenvironment consists of extracellular matrix, stromal cells (such as fibroblasts, mesenchymal stromal cells, pericytes, occasionally adipocytes, and blood and lymphatic vascular networks), and immune cells (including T and B lymphocytes, natural killer cells, and tumour-associated macrophages) [55]. Thus, in addition to tumour cells themselves, other components of the tumour microenvironment can be targeted by SC-based therapy.

### Pro-apoptotic and antiproliferative proteins

The SCs can be modified using viral and nonviral methods allowing the secretion of specific anticancer proteins. Due to its low host immunogenicity, the nonviral cell-penetrating peptide-conjugated protein delivery is an excellent tool for biologically active, defined protein delivery and may have important clinical applications for the use of clinical SC-based therapy [56]. In this case, anticancer proteins comprise both pro-apoptotic and antiproliferative proteins.

Pro-apoptotic proteins include the tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) that binds both the death receptors DR4 (TRAILR1) and DR5 (TRAILR2), specifically expressed by cancerous cells, to initiate caspase-mediated apoptosis [57]. The antitumoural potential of modified NSCs and MSCs for secretable TRAIL (S-TRAIL) has been demonstrated in mouse tumour models of both nodular and invasive GB [58,59]. Recent studies have demonstrated that the combined effect of the anti-apoptotic protein B-cell lymphoma 2 (Bcl2) downregulation and S-TRAIL-induced apoptosis results in an efficient regression/eradication of gliomas [60,61]. To upregulate the SC TRAIL expression, adipose-derived SCs were engineered with biodegradable polymeric nanoparticles (NPs; see section ''Nanoparticles").

Antiproliferative proteins include biological agents preventing the binding of endogenous ligands to their cognate receptors, such as the epidermal growth factor (EGF) to its receptor variant III ($EGFR^{vIII}$), constituting the perfect therapeutic target for GB [62]. Consequently, the inhibition of the proliferation of cancerous cells was found [63,64]. Among the number of antiproliferative molecules, a limited number of molecules can be secreted in the extracellular milieu. In various preclinical cancer models, interferons α (IFN-α) and β (IFN-β) regulate the tumour cell grow. In a recent study, when the effect of a typical cytokine

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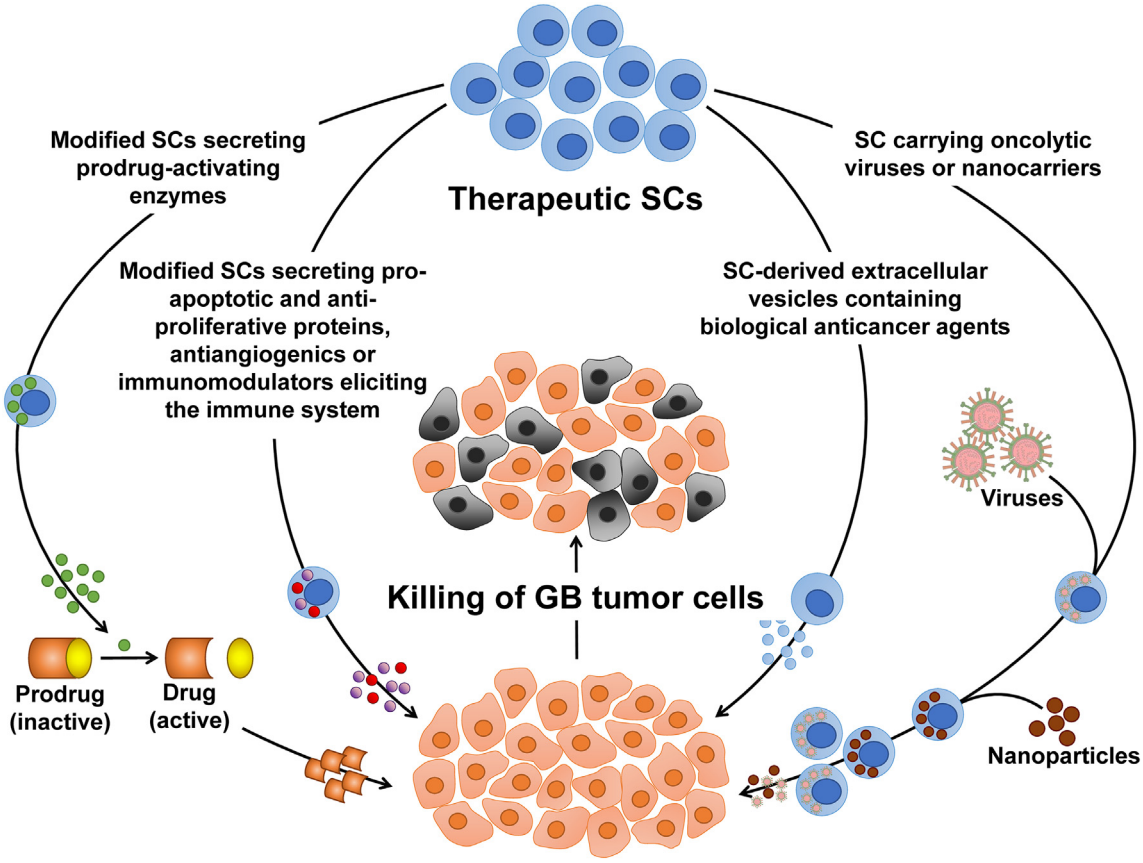


**Fig. 2** Strategies for the use of modified stem cells (SCs) and SC-released extracellular vesicles expressing/carrying different antitumour payload against glioblastoma (GB).

expressed by therapeutic SCs, such as INF-β, was assessed by a systemic administration route in mice bearing GB, a regression of tumour growth was obtained [65]. Bone morphogenetic proteins (BMPs) also can decrease tumour growth by activating their cognate receptors (BMPRs). The secretion of BMP4 by human adipose-derived MSCs suppresses the tumour growth and prolongs the survival of mice bearing GB [66,67]. SC proteins provoking cell cycle arrest, such as growth arrest specific-1 (Gas1), also induce an antitumoural effect against GB [68].

## Drug-activating enzymes

The SC-mediated suicide therapy involves engineered SCs secreting an enzyme that catalyses the conversion of a nontoxic prodrug into a cytotoxic drug, which induces the cell death of the brain tumour cells by the bystander effect [69]. Herpes simplex virus thymidine kinase (HSV-TK) and cytosine deaminase (CD) are examples of genes encoding enzymes that can convert prodrugs ganciclovir (GCV) and 5-fluorocytosine (5-FC), respectively, into drugs that are cytotoxic for tumours [70,71]. After transfection of GB cells of previously untreated patients with the HSV-TK gene and subsequent systemic treatment with nontoxic GVC, the encoding product of HSV-TK gene (thymidine kinase) phosphorylates GCV to cytotoxic GCV triphosphate (GCV-TP) to block DNA replication [72]. Based on this outcome, HSV-TK has been used in modified MSCs and NSCs to reduce the tumour growth in animal models bearing GB [73,74]. Several preclinical *in vitro* and *in vivo* studies, as well as clinical trials enrolling GB patients, have confirmed the efficacy of modified NSCs and MSCs secreting CD when associated with the oral administration of 5-FC [71,75]. Recently, it was found that polylysine-modified polyethylenimine copolymer can be used to transfect MSCs with the TK gene for combinational suicidal gene therapy in GB [76].

## Antiangiogenics

The intravenous administration of antiangiogenic agents transiently normalises the abnormal vasculature, thus decreasing tumour-associated vasogenic brain oedema and, in turn, resulting in profitable effects against GB [77]. Both the increasing pericyte coating of the small vasculature and the decreasing vessel diameter/permeability induce an antiangiogenic effect [51,52]. The expression of pericyte markers by MSCs and their ability to home to tumour vasculature makes them useful to decrease tumour angiogenesis [79,79]. Engineered SCs expressing antiangiogenic agents can be useful to suppress the tumour growth by creating a hostile, nonpermissive microenvironment [16]. For example, NSCs that are modified to express all three type 1 repeats (3TSR) of thrombospondin 1 (TSP-1) induce dramatic reduction of tumour vessel density, which

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results in an inhibition of tumour progression and increased survival in mice bearing highly malignant human gliomas [80]. As TSP-2, TSP-1 exerts its direct effect through CD36, CD47, and β1 integrins, which collaborate to transmit the thrombospondin signal. Furthermore, these receptors appear to associate with VEGFR2 to form a platform for the integration of positive and negative signals for angiogenesis. The cross-talk between pro- and antiangiogenic signal transduction pathways may enable TSP-1/-2 to inhibit angiogenesis by antagonising survival pathways while also activating apoptotic pathways [81].

## Pro- and anti-inflammatory factors

Interleukins (ILs) regulate immune and inflammatory responses and exert antitumoural effects [82]. SCs-based therapies via increased levels of IFN-γ, activation of natural killer cells, and recruitment of tumour-specific T cells lead to substantial prolongation of survival in patients with malignancies [16]. NSC IL-12, IL-4, or IL-23 lead to robust T-cell accumulation along with the tumour as well as within tumour microsatellites, markedly reducing their growth [85–86]. Human MSCs expressing IL-12 or IL-18 have shown high efficiency to regress GB [88,87].

Immunotoxin therapy is emerging as a promising strategy to tackle brain malignancies including GB. Immunotoxins are chimeric proteins consisting of a cytotoxic molecule (e.g., *Pseudomonas* and *Diphtheria* toxins) linked to a monoclonal antibody or a growth factor targeting a specific cancerous cell marker [88]. Immunotoxins that can reduce the inflammatory activities of the host immune system [89] are considered as positive immunomodulators. The major limitations of using immunotoxins for clinical applications include: (a) poor penetration capability due to which optimal concentration in the tumour is rarely reached; (b) neural toxicity; and (c) elicitation of the immune response, which limits the number of administration cycles [90]. SCs are the best candidate to deliver immunotoxins, overcoming these challenges. *Pseudomonas* exotoxin blocks protein synthesis by catalysing the inactivation of elongation factor-2 (EF-2); thus it has been used as an antitumoural agent. SCs engineered to express IL13-*Pseudomonas* exotoxin have been employed to target the IL-13 receptor or EGFR expressed by GB [91]. Human bone marrow-derived MSCs, engineered to secrete the ephrin receptor A2 (EphA2)-specific immunotoxin, have shown *in vitro* and *in vivo* a killing effect against glioma cells [92]. The antiangiogenic effect of VEGF-PE38 targeting VEGFR expressed by glioma vascular endothelial cells was also proved [94,93]. Thus, surprisingly, when human bone marrow-derived MSCs were engineered to secrete $VEGF_{165}$-EphA1 conjugated with a truncated portion of *Pseudomonas* exotoxin A termed PE38 ($VEGF_{165}$-EphA1-PE38) to target both vascular endothelial and vascular mimicry in GB, a considerable tumour growth reduction was found [94].

## Nanoparticles

Due to their potential to enhance the bioavailability of often insoluble chemotherapeutic agents in the tumour site, NP-based DDSs are novel therapeutic and diagnostic engineered technologies for cancer treatment [95]. NPs offer many advantages as DDSs such as increasing the half-life of drugs by evading the reticuloendothelial system [96]. Additionally, NPs can be functionalised with different biological molecules, peptides, antibodies, and protein ligands. These systems include a hydrophilic central core, a target-oriented biocompatible outer layer, and a middle hydrophobic core where the drug destined to reach the target site resides. Most of the NPs maintain their structural shape and are constructed according to the cancer microenvironment [97]. However, NP-based DDSs still have many limitations to be addressed, such as poor oral bioavailability, instability in circulation, inadequate tissue distribution, and toxicity [100,99]. Most of these disadvantages can be overcome by using SCs as a carrier to load NP-based DDSs [100]. In a proof-of-principle study, Roger et al. [101] employed MSCs carrying with great efficiency two types of nanocarriers, polylactic acid NPs and lipid nanocapsules loaded with coumarin-6 (fluorescent probe used to conduct *in vivo* tracking, cell uptake, and transport mechanism studies of drug DDSs), which accumulated preferentially in the tumour site. Interestingly, MSCs were found to be able to deliver NP-based DDSs in brain tumours. Clavreul et al. [102] made MSCs carrying lipid nanocapsules loaded with the organometallic complex ferrociphenol (Fc-diOH), a cytotoxic drug, which exerted an *in vitro* and *in vivo* anticancer activity against glioma cells. Besides MSCs, NSCs also allow the tumour-selective distribution and retention of NPs within invasive brain tumours [103]. In 2016, to enhance the SC TRAIL expression, human adipose-derived SCs were engineered with biodegradable polymeric NPs. TRAIL DNA was bound to hydrolytically biodegradable polymers, amine end-modified poly(ß-amino ester)s, thereby allowing condensed DNA in the form of NPs. Results demonstrated a considerable upregulation of TRAIL in polymeric nanoparticle-engineered human adipose-derived SCs, which were transfected with the plasmid vector encoding the native full-length TRAIL, compared with those transfected with the bare plasmid [104]. Cheng et al. [105] coated NSCs with pH-sensitive doxorubicin-loaded mesoporous silica NPs (MSNs-Dox). These NP conjugates provided a delayed drug-releasing mechanism and allowed NSC migration towards a distant tumour site. NSCs could undergo cell death and release impregnated MSNs-Dox, which subsequently induced toxicity against the surrounding glioma cells. The release of NPs from SCs occurs by membrane rupture, caused by cytosolic accumulation, or by photo-/hyperthermia-induced cell death [106]. According to these findings, SCs carrying NP-based DDSs have great potential to treat brain malignancies such as GB.

## Oncolytic viruses

Oncolytic viruses (OVs) are natural or genetically modified viruses that can selectively replication within tumour cells, lyse them, and/or elicit the immune system recognition [107]. However, the inadequate distribution of OVs inside a tumour, low infectivity by cancerous cells, and rapid inactivation by the immune system of the host are the major points of concern to be addressed [110,109]. Tumour tropism of SCs (see section ''Tumour tropism'') may be utilised

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to deliver OVs towards tumour sites without eliciting the immune system of host [110]. Both NSCs and MSCs are effective vehicles able to deliver OVs against tumours, consequently prolonging the survival rate of the receiving glioma animal models [87,89–92]. NSCs were transfected with a gliomatropic oncolytic adenovirus, the conditionally replication-competent adenovirus driven by the survivin promoter (CRAd-S-pk7), to target cells overexpressing survivin, a protein highly expressed in glioma cells and upregulated by radiation therapy [111].

### Extracellular vesicles

Extracellular vesicles (EVs) are cell-released vesicles containing lipids, nucleic acids, and proteins. According to their size and mode of production, EVs can be divided into microvesicles (MVs) and exosomes (EXs). MVs, typically ranging 50–1000 nm in diameter, originate from the outward budding of the plasma membrane, whereas EXs, typically ranging 30–100 nm in diameter, originate from the inward budding of the limiting membrane of multivesicular bodies, leading to the generation of intraluminal vesicles [112]. EVs play an important role in mediating intercellular signalling in both physiological and pathological conditions [112], such as transferring biological molecules from donor cells (e.g., MSCs) to both neighbouring and distant cells [113]. Because of the ability of MSCs to release EVs, they are natural and living carriers of biological anticancer payloads, such as therapeutic miRNA, siRNA, and chemotherapeutic molecules. MSCs engineered to shed EXs containing the miRNA miR-7, which control cell proliferation and apoptosis in tumours, were investigated for their potential to prime resistant tumour cells to induce apoptosis in brain tumours like GB. When miR-7-enriched EXs released from MSCs were transferred into GSCs, both the tumour regression and upregulation of death receptor ligand in resistant GB cells were obtained. miR-7 significantly decreased the tumour volume, especially when derived from MSCs expressing S-TRAIL [114]. MSC-derived EXs can deliver anticancer drugs such as paclitaxel to prolong the survival of mice bearing GB [115].

## Strategies to improve the anticancer efficacy of stem cell-based therapy

Various strategies could be employed to improve the therapeutic potential of SCs. The improvement of the immunotolerance and the tumour tropism/homing of SCs, as well as the optimal choice of administration route, together with combinational approaches, are strategies all aimed to increase the anticancer efficacy of SCs.

### Improvement of the stem cell immunotolerance

Allogenic SC rejection, even in the immunocompetent patients, is not yet an entirely resolved issue of SC-based therapy [116]. The knockout of the human leukocyte antigen class I gene prevents the rejection of HSCs, thus increasing their survival [117]. Although not easily obtainable, autologous NSCs are considered the best SCs for the treatment of gliomas because of their ability to avoid immune system-based rejection [118]. Bagó et al. [2] transdifferentiated human fibroblasts into tumour-homing early-stage induced NSCs (h-iNSC$^{TE}$) and engineered them to express TK or TRAIL. The assessment of these SCs in animal models with GB revealed that they were able to avoid the immune rejection which, in turn, could maximise the treatment durability in further human trials. The disruption of the T-cell costimulatory or the activation of T-cell inhibitory pathways by knocking out the cytotoxic immunoglobulin T-lymphocyte-associated protein 4 (CTLA4) and the programmed cell death ligand 1 (PDL1) are effective approaches to prevent immune rejection, especially of human ESC-derived allografts [119].

### Enhancement of the stem cell tumour tropism/homing

Overexpression of the SC migratory molecules allows the enhancement of SC tumour tropism/homing. For instance, overexpressing chemokine receptors in SCs has proved to be successful in increasing chemokine-directed migration towards intracranial gliomas [120]. Pulukuri et al. [121] found that histone deacetylase inhibitors result in the overexpression of the urokinase plasminogen activator in MSCs, thus enhancing their migratory ability towards the tumour site. Hypoxia is a hallmark of malignant tumours that correlates with increased tumour aggressiveness and poor treatment outcomes. To exploit this mechanism for targeting tumour hypoxia, Jiang et al. [122] developed polymeric NP-induced CXCR4-overexpressing human adipose-derived SCs (hADSCs). Interestingly, when injected in the contralateral brain in a mouse intracranial GB xenograft, these CXCR4-overexpressing hADSCs exhibited long-range migration towards GB and preferentially penetrated the hypoxic tumour core.

### Optimal choice of the stem cell administration route

An important factor influencing the anticancer efficacy of SC-based therapy is the administration route chosen to optimally deliver SCs towards the tumour site. Intraventricular route is much better than intravenous or intraperitoneal administration route [123]. Intranasal delivery is a new method that provides an extraordinary approach to overcoming the existing barriers of SC delivery for the treatment of intracerebral gliomas [127,125]. The implantation of encapsulated SCs into the resection cavity is another novel strategy to improve the therapeutic effectiveness of SCs. The encapsulation of SCs within biocompatible and semipermeable scaffolds occurs by using biodegradable hydrogels and synthetic materials composed of hyaluronic acid, alginate, agarose, and other polymers [126]. The enhancement of the cell survival and the prevention of a substantial rapid ''washout'' of cells by the cerebrospinal fluid are the main advantages of SC encapsulation [126]. Using a mouse model of GB surgical resection/recurrence, a biocompatible electrospun nanofibrous scaffold encapsulating TRAIL-expressing human MSCs increased, with respect to the

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standard direct injection, five-fold the retention in the surgical cavity and three-fold the persistence of cells [127].

### Combinational approaches

GB comprises heterogeneous cell populations that are genetically and epigenetically unstable [128]. Therefore, combinational approaches might exert an antitumour effect more effectively against GB when considered as a multicellular system. The number of studies about SCs engineered to secrete different therapeutic agents, which target various signalling pathways in cancerous cells is growing [129]. Co-expression of IL-18 and IFN-β, two immune-stimulatory cytokines, by therapeutic SCs proved to be a successful strategy in animal models with GB [23]. Antibody fragments such as single-chain variable fragments and nanobodies or variable domains of heavy-chain only antibodies bind epitopes overexpressed on tumour cells and give rise to bifunctional proteins that can disturb signalling pathways in cancerous cells [130]. Pro-apoptotic TRAIL protein was fused to a nanobody targeting EGFR to obtain the immune-conjugate Enb-TRAIL. Enb-TRAIL decreases the tumour growth resulting in caspase-mediated cell death by the suppression of EGFR signalling and activation of death receptors. In mouse models of GB, the expression of ENb-TRAIL by NSCs causes a considerable tumour regression, resulting in the prolongation of survival [63,134]. Different studies have proved that various drugs synergise with SC-based therapy [57,135]. Valproic acid enhances the antitumour effect of MSC-mediated HSV-TK gene therapy in intracranial glioma [133]. Similarly, the co-administration of temozolomide with MSCs expressing TRAIL or INF-β was more effective to regress GB [137,135]. Recently it was found that panobinostat, a histone deacetylase inhibitor, potentiates the therapeutic effects of MSCs exhibiting TRAIL [136]. The combination of radiotherapy, temozolomide, and NSCs carrying OV reportedly increased the survival of mice bearing GB patient-derived xenografts [137].

## Utility and limitations of stem cell-based therapy

### Application of stem cells as a diagnostic tool

By virtue of their tumour tropism, probe-labelled SCs could be exploited to diagnose tumour bulks. In particular, they could be utilised to quantify the tumour infiltration into

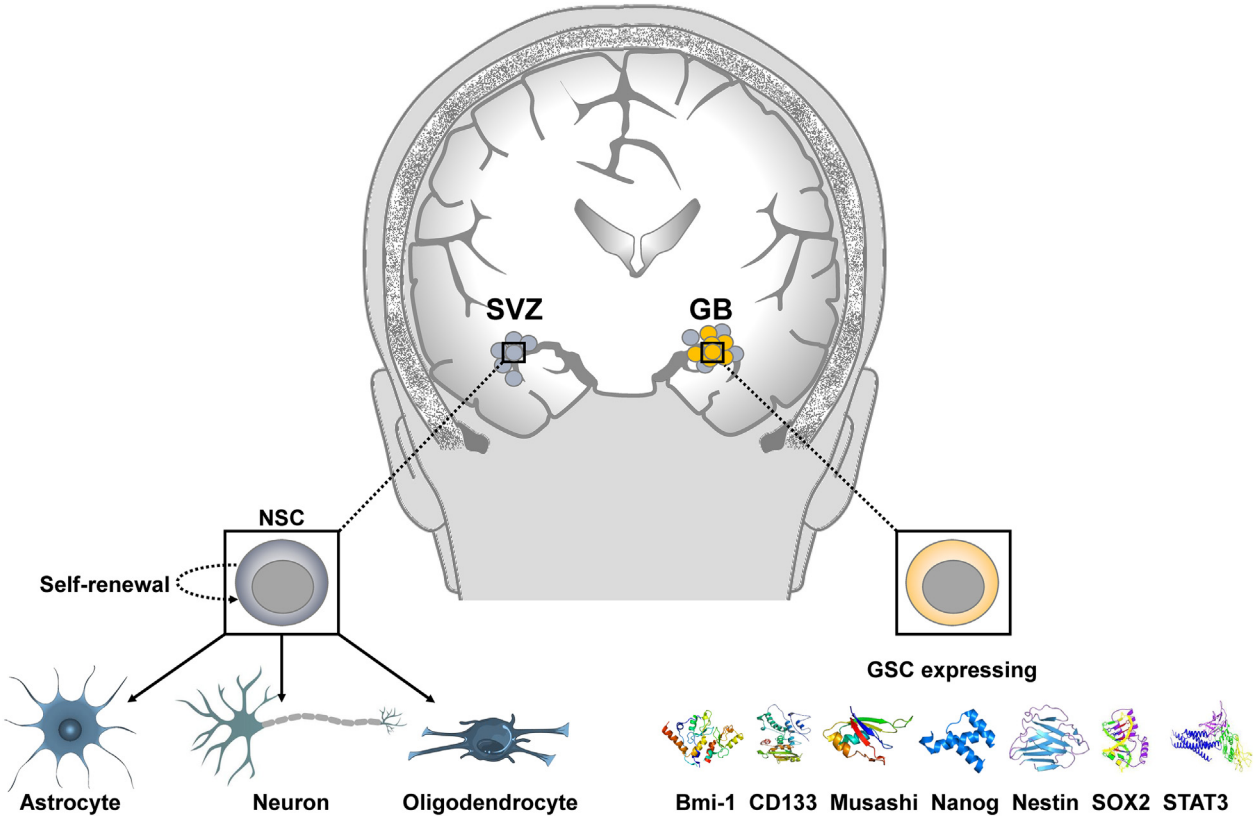


**Fig. 3** Localization of cancer stem cells (CSCs) in glioblastoma (GB). Subependymal ventricular zone (SVZ) represents the classic neurogenic niche where neural stem cells (NSCs) reside. Herein, NSCs can undergo self-renewal or differentiate into astrocytes, neurons, and oligodendrocytes. Glioma stem cells (GSCs), which harbour tumour-initiating potential, share several core properties of NSCs, such as stemness and sustained proliferation. These GSCs can be identified through specific cell markers, such as B lymphoma Moloney murine leukaemia virus insertion region 1 homolog (Bmi-1), cluster of differentiation 133 (CD133), Musashi RNA-binding proteins, neuroepithelial SC protein (Nestin), as well as homeoprotein Nanog, sex-determining-region-Y-like high-mobility group box 2 (SOX2), and signal transducer and activator of transcription 3 (STAT3) transcription factors.

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**Table 1** Selected Stem Cell Trials Involving Neural Stem Cells in Glioblastoma.

| NCT identifier (ClinicalTrials.gov) | Type of trial | Purpose | Intervention | IPrimary outcome measure | Trial status | Sponsor and collaborators |
|---|---|---|---|---|---|---|
| NCT03072134 | Phase I | NSC-based virotherapy in combination with standard radiation and chemotherapy for patients with newly diagnosed malignant glioma | Biological: NSCs loaded with an oncolytic adenovirus | Determine the maximum number of NSCs loaded with the oncolytic adenovirus | Completed | Northwestern University |
| NCT02015819 | Phase I | To determine the feasibility of treating study patients with more than one dose of NSCs followed by 7-day courses of 5-FC and leucovorin | Biological: *E. coli* CD-expressing genetically modified NSCs<br>Drugs: 5-FC, leucovorin calcium | Incidence of all adverse events, toxicities, and allergic reactions | Active, not recruiting | City of Hope Medical Center, National Cancer Institute |
| NCT01172964 | Phase I | To determine the safety and feasibility of intracerebral administration of NSCs in combination with oral 5-FC in patients with recurrent high-grade gliomas | Biological: *E. coli* CD-expressing genetically modified NSCs<br>Drug: 5-FC<br>Procedure: therapeutic conventional surgery | Determination of the safety and feasibility by measuring clinically symptomatic intratumoural haemorrhage, CNS infection, seizures, altered mental status, development of focal neurologic deficits, as well as chemotherapy-associated toxicities | Completed | City of Hope Medical Center |
| NCT02055196 | Phase I | To determine the biologic activity of the hCE1m6-NSCs by comparing SN-38 concentrations in the brain after treatment with hCE1m6-NSCs and irinotecan compared to irinotecan alone | Biological: allogeneic NSCs expressing carboxylesterase<br>Drug: irinotecan hydrochloride | Incidence of all attributable toxicities and biologic activity | Withdrawn | City of Hope Medical Center, National Cancer Institute |
| NCT02192359 | Phase I | To define the RP2D of intracranially administered allogeneic NSCs expressing hCE1m6 in combination with intravenous irinotecan in patients with recurrent high-grade glioma | Biological: allogeneic NSCs expressing hCE1m6<br>Drug: irinotecan | Incidence of all attributable toxicities and DLTs | Recruiting | City of Hope Medical Center, National Cancer Institute |

*Note*. 5-FC = 5-fluorocytosine; CD = cytosine deaminase; CNS = central nervous system; DLTs = dose-limiting toxicities; *E. coli* = *Escherichia coli*; hCE1m6 = human liver carboxylesterase; NCT = national clinical trial; NSCs = neural stem cells; RP2D = recommended phase II dose; SN-38 = 7-ethyl-10-hydroxycamptothecin.

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the healthy brain parenchyma as well as their precise tracking. For instance, as shown in Fig. 3, some cell markers expressed by GSCs could be employed to localise them during SC-based therapy for GB. To date, diagnostic methods include magnetic resonance imaging (MRI) and positron emission tomography imaging. MRI allows to visualise NSCs and MSCs labelled with lipophilic dye-coated superparamagnetic particles reaching intravenously rat malignant gliomas [83]. Ferumoxytol-labelled human NSCs detected by MRI is currently under phase I clinical trial [138]. Positron emission tomography is another imaging detection method of therapeutic SCs highly sensitive [139]. Bioluminescence-based imaging is utilised to trace luciferase gene-transduced MSCs and NSCs in the breast, ovarian, lung, and brain tumours [105—105]. Luciferase-labelled NSCs carrying S-TRAIL allow monitoring/delivery of anticancer proteins to GB cells [59]. Semiconductor quantum dots and fluorescent NPs can be utilised instead of luciferase to label NSCs [144,141]. Also, MSNs could be used as diagnostic agents for the imaging of SCs via single-photon emission computed tomography [142].

### Tumourigenic potential of stem cells

A major point of concern among the scientific community that remains regarding anticancer SC-based therapy is their putative tumorigenesis. The spontaneous malignant transformation occurs in 45.8% of bone marrow-derived MSCs kept in culture for long periods (5—106 weeks). The culture condition is one of the most important factors affecting genomic instability and subsequently malignant transformation of SCs [143]. Oxygen tension is another factor influencing SC transformation [144]. Most studies have shown that multipotent NSCs, MSCs, and HSCs are more stable than pluripotent ESCs and iPSCs; therefore, they are more suitable for therapeutic purposes [15].

### Other detrimental effect of stem cells

As discussed in section ''Improvement of the stem cell immunotolerance", the immunomodulatory activity of SCs might be beneficial for tumour cells to escape immune surveillance [2]. Such engineering effort could be a double-edged sword as it may also attenuate antitumour immune reaction at the site where therapeutic SCs are recruited [145]. Besides, unwanted tissue damage may occur by modified SCs that are loaded with cytotoxic agents when these SCs home to nontumour sites [111].

## Conclusion

SC therapy is emerging as a potentially revolutionary and novel strategy in GB treatment. As extensively discussed above, due to their intrinsic tumour tropism, SCs are particularly adapted for delivering anticancer agents to tumour sites. To overcome the short half-life of conventional DDSs, SCs and SC-released EVs can be employed to express/load different antitumour payloads. Furthermore, SCs can be exploited to diagnose brain tumour bulks.

Among all types of SCs, NSCs demonstrated the greatest therapeutic potential against GB. iPSC-derived NSCs home to human and mouse GB cells in culture, as well as syngeneic GL261 GB xenografts *in vivo* [146]. These studies suggest that NSCs created by the conversion of iPSCs are tumour-homing drug carriers with the potential to deliver anticancer agents to treat GB. The efficacy of NSCs carrying anticancer payloads against GB has been confirmed in several clinical trials. Recent/past ongoing clinical trials involving NSCs for GB are mentioned in Table 1.

However, anticancer SC-based therapy has still many issues that need to be addressed, such as the choice of the suitable therapeutic transgene, the optimal route of administration, the poor *in vivo* viability/survivor, the biosafety (e.g., the putative malignant transformation of some types of SCs), and the antitumour immune response attenuation of SCs. The resolution of these issues, combined with the biological understanding of the interaction between SCs and GB, will improve as soon as possible with the anticancer efficacy of SC-based therapy, which may be used by clinicians of tomorrow not only to extend the survival but to also permanently cure GB patients.

## Authors' contributions

All authors reviewed the literature. MAZ and CV wrote the manuscript. CV made the critical revision and drew the figures. All authors contributed to the intellectual content of this paper and approved the final manuscript. No funding was received from any source.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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