

# The impact of stem cells in neuro-oncology: applications, evidence, limitations and challenges

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**Abstract.** *Background:* Stem cells (SCs) represent a recent and attractive therapeutic option for neuro-oncology, as well as for treating degenerative, ischemic and traumatic pathologies of the central nervous system. This is mainly because of their homing capacity, which makes them capable of reaching the inaccessible SC niches of the tumor, therefore, acting as living drugs. The target of the study is a comprehensive overview of the SC-based therapies in neuro-oncology, also highlighting the current translational challenges of this type of approach. *Methods:* An online search of the literature was carried out on the PubMed/MEDLINE and ClinicalTrials.gov websites, restricting it to the most pertinent keywords regarding the systematization of the SCs and their therapeutic use for malignant brain tumors. A large part of the search was dedicated to clinical trials. Only preclinical and clinical data belonging to the last 5 years were shortlisted. A further sorting was implemented based on the best match and relevance. *Results:* The results consisted in 96 relevant articles and 31 trials. Systematization involves a distinction between human embryonic, fetal and adult, but also totipotent, pluripotent or multipotent SCs. Mesenchymal and neuronal SCs were the most studied for neuro-oncological illnesses. 30% and 50% of the trials were phase I and II, respectively. *Conclusion:* Mesenchymal and neuronal SCs are ideal candidates for SCs-based therapy of malignant brain tumors. The spectrum of their possible applications is vast and is mainly based on the homing capacity toward the tumor microenvironment. Availability, delivery route, oncogenicity and ethical issues are the main translational challenges concerning the use of SCs in neuro-oncology. ([www.actabiomedica.it](http://www.actabiomedica.it))

**Key words:** Cell-Based Therapy, High-Grade Glioma, Neuro-Oncology, Somatic Cell Therapy, Stem Cells

## Background

A large part of modern neurology rests on the seminal work of Santiago Ramón y Cajal, which in 1913, demonstrated for the first time in the history of medicine that neurons can regenerate equally to other tissues (1-3). Since that time, this along with other pivotal points, has led to several steps forward in a better understanding of the pathophysiology of several illnesses affecting the central nervous system (CNS)

(4-10). More recently, in the CNS as in other systems and tissues, the regenerative property was clarified as being attributable to the existence of 'stem cells' which, by definition, are immature undifferentiated cells having a capacity of self-renewal. The self-renewal capacity practically consists in the fact that one of the two daughters arising from the progenitor cell can differentiate into any other specialized cell of a given tissue, with the remaining one instead maintaining the tissue-specific stem cell heritage. The possibility of growth,

regeneration and repair of a given tissue is entirely attributable to the subsistence of this cellular population, which seems to hold and play regulative functions, while also being subject to a functional control within its specific microenvironment, also referred to as 'niche' (11-22). Currently, no field of medicine can be thought as immune to the enthusiasm coming from the potential applications of stem-cell therapy, which can currently be considered the fully-fledged backbone of regenerative medicine.

The neuro-oncological field has been among the first to be interested in the stem cell revolution, mainly because of the kinetic and qualitative aspects which this specific cellular population has in common with tumors, namely, the high replicative rate, lack of contact inhibition, as well as capability to origin teratocarcinomas in mice, to cite just a few. However, in recent years, the explosive volume of the literature about the use of stem cells in any field of neuroscience, on one hand, and the dramatic increase in the qualitative and quantitative spectrum related to the stem cells on the other, have unavoidably led to confusion, especially regarding the line between the preclinical and clinical level of evidence.

This study is aimed at an updated and comprehensive overview of the theoretical and practical impact of the stem cell-based therapies in neuro-oncology, along with the assessment of their clinical level of evidence, limitations and future challenges.

## Methods

An online search of the literature was carried out on the PubMed/MEDLINE (<https://pubmed.ncbi.nlm.nih.gov>) and ClinicalTrials.gov websites (<https://clinicaltrials.gov>). On PubMed/MEDLINE, both the MeSH (Medical Subject Headings) database and free mode search were used to carry out a search of the literature combining the following keywords: "Stem Cells" [MeSH], "Cell- and Tissue-Based Therapy" [MeSH], "Regenerative Medicine" [MeSH], "Cell Engineering" [MeSH], "Genetic Therapy" [MeSH], "Gene Transfer Techniques" [MeSH], "Central Nervous System" [MeSH], "Brain" [MeSH], "brain tumors" [text word] and "Stem Cells" [text word]. "Classification criteria",

"clinical employment" and "therapeutic use" were the subheadings of the MeSH database search. Only articles in English or translated into English, published in the last five years, and regarding the field of neuro-oncology were selected. Based on the best match and relevance inferred by the titles and summaries, a further sorting was carried out.

On the ClinicalTrials.gov finder, the search terms "Brain tumors" and "Stem Cells" were used in the "condition/disease" and "other terms" fields, respectively. No restriction for country, recruitment status and study phase were applied. A brief summary of the retrieved trials was reported focusing on the status and phase, separately from the results.

## Results

### 1. Volume of the Literature

The search returned a total of 1,802 articles and 81 clinical trials. After the implantation of the exclusion criteria and removal of duplicates, 96 relevant articles and 31 trials were sorted.

### 2. Overview and Systematization of the Stem Cells

#### 2.1 Origin

Based on their origin, stem cells may be classified as embryonic, fetal or adult.

Human embryonic stem cells (h-ESCs) originate from a blastocyst inner cell mass. They hold atypical cell cycle regulation, which explains their unlimited potential of propagation in culture, specific set of markers, lack of contact inhibition and maximal potential of differentiation (14, 23-27). Typically, they are known to form teratocarcinomas in nude mice (23, 28-30).

Fetal stem cells come from fetal blood and fetal tissues and form blood cells, tissues and organs. Umbilical cord blood, veins and matrix are sources of fetal stem cells, along with the amnion and placenta. Umbilical cord fetal stem cells have yielded great interest because they are readily available, inexpensive, multipotent and immune from ethical issues (31-36).

Adult stem cells are present in all differentiated tissue (37-39). They were isolated for the first time in the hematopoietic system, but subsequently also in the adult CNS (40-44). Adult stem cells have been reported to have tremendous plasticity and an equally extensive regenerative capability. The main strength of this type of stem cell lies, first, in its theoretically high availability for autologous transplantation, and second, in its absence of immunological complications (45, 46).

## 2.2 Plasticity

Stem cells may also be classified according to their plasticity. This systematization entails the distinction between totipotent, pluripotent or multipotent cells.

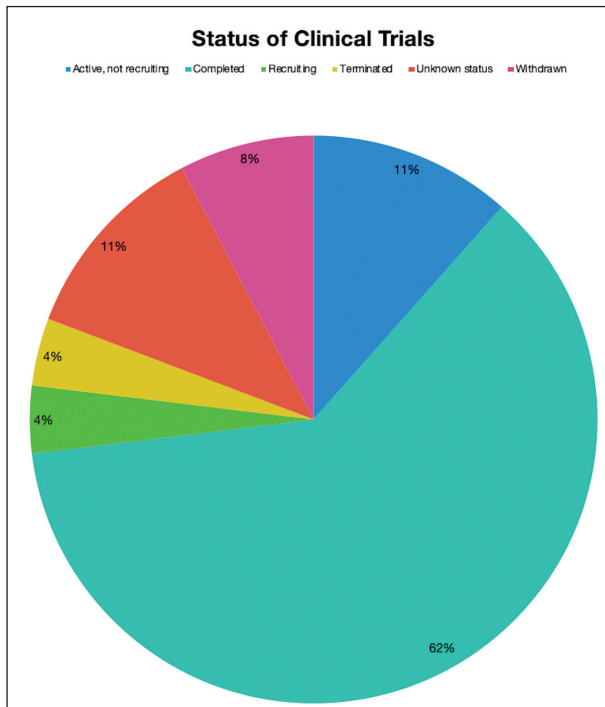
In principle, the sole and unique totipotent cell is the zygote along with its progeny (47). Every somatic cell, embryonic and extra-embryonic tissue included, comes from the totipotent progenitor cell. In contrast, the pluripotent cell, also referred to as h-ESCs, since it originates from the blastocyst inner cell mass, may stem from all three of the germ layers, giving birth to ectodermal, mesodermal and endodermal tissues, but it does not stem from embryonic or extra-embryonic tissue (22, 48). Multipotent cells, belonging to the three germ layers even in the embryonic stage, are capable of giving birth to a vast amount of cell lineage which, in the past, was thought to generate lines belonging exclusively to the same tissue where they reside. Nevertheless, this assumption has been recently questioned (49). Being present also in the adult age, multipotent cells sustain auto-regeneration and allows tissues to repair themselves after damage. There are four known main types of human multipotent cells, namely, mesenchymal stem cells (h-MSCs), neural stem cells (h-NSCs), bone marrow stromal cells, and olfactory ensheathing cells. Within the CNS, h-NSCs have been isolated from the three sites capable of a neuronal turnover *par excellence*: the adult ventricular-subventricular zone, the olfactory bulb and the hippocampus (50, 51). At these sites, h-NSCs have been proven to differentiate into neurons, astrocytes and oligodendrocytes, as well as being responsible for the maintenance of the homeostatic and regenerative processes (52, 53). The h-NSCs hold a restricted neural differentiation capability, which is practically committed to specific subpopulation line-

ages (54-60). Both adult h-NSCs and h-ESCs are related to specific biomarkers of embryogenesis and adult neurogenesis (61). A further, more recent class of stem cells is represented by the human-induced pluripotent staminal cells (h-iPSCs). They derive from genetically reprogrammed adult somatic cells, thus making them theoretically unlimited in number. They also have proven to have the same potential of pluripotent cells (62-64). Both of these aspects account for the reasons why h-iPSCs have aroused the maximum interest among all stem cells, being that there is a theoretically inexhaustible source of pluripotent cells.

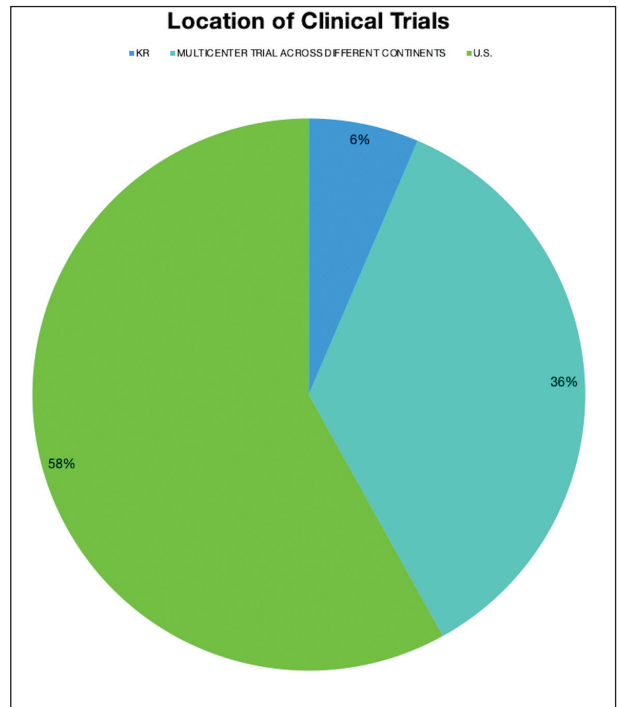
## 3. Evidence on the Effectiveness and Safety in Neuro-oncology

The highest clinical level of evidence about the effectiveness of stem cell-based therapy consisted in 31 clinical trials, for a total of 1,103 patients recruited, summarized in Table 1 (Suppl Table). Of these, 30% were phase 1, 50% phase 2 and 7% phase 3 (Graph 1). Most of the trials were executed in the U.S. (60%), whereas 32% were multicentric (Graph 2). To date, only 64% were completed (Graph 3). In 24 trials (77.4%), peripheral blood stem cells, namely hematopoietic cells, were involved, with the aim of assessing their effectiveness in counteracting the myeloablative effects of the chemotherapy against malignant brain tumors. In 4 trials (12.9%), h-NSCs were tested basically as carriers for oncolytic viruses (3.2%), or also as drugs in a genetically modified form (9.6%). In 2 further trials, tumor-derived stem cells were used for a vaccine (Graph 4). In all cases, stem cells were used in association with a defined chemo-radiotherapy protocol considered as standard of care. Only 2 trials have tabular results available. Both of them studied the effectiveness of radiation therapy in achieving a significant increase of progression-free survival and overall survival of glioblastoma, secondary to the inclusion of tumor peripheral margin encompassing the tumor stem cells. Both were able to prove that this strategy adds benefits and has a good safety profile.

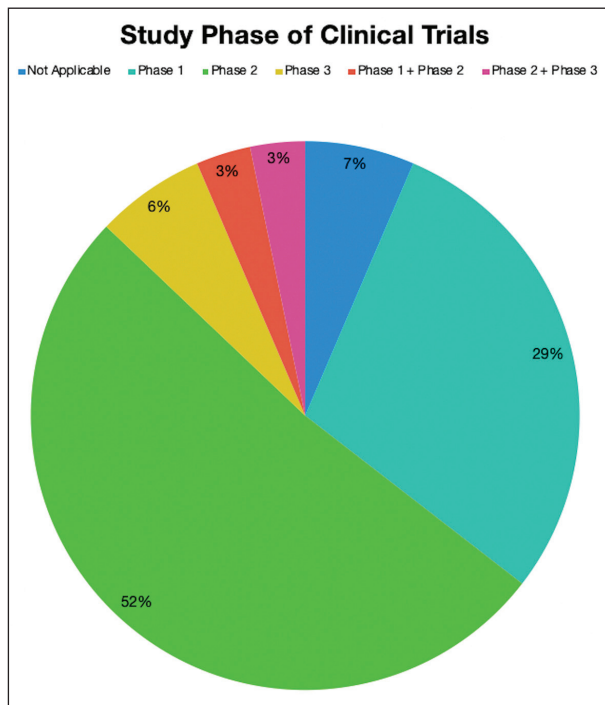
Most of the evidence about the effectiveness of the h-NSCs-based therapy, however, belongs to a pre-clinical level (65-74). Apart from h-NSCs, h-MSCs also have been widely tested for their potential use in



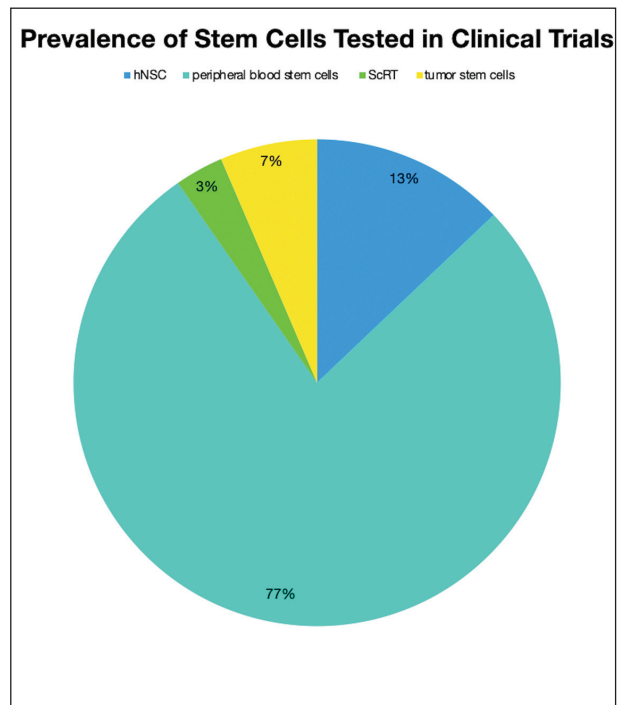
**Graph 1.** Pie graph showing the distribution of the clinical trials according to the status



**Graph 3.** Pie graph showing the distribution of the clinical trials according to the location



**Graph 2.** Pie graph showing the distribution of the clinical trials according to the study phase



**Graph 4.** Pie graph showing the distribution of the type of stem cell tested

the treatment of CNS malignancies, often with positive results being obtained in animals (75, 76).

## Discussion

The rationale at the base of the use of stem cells for treating malignant CNS tumors lies in various aspects. These cells are theoretically capable of: surrounding the glioblastoma and inhibiting the spreading of the tumor (77, 78); being selective deliverers of drugs (79); transferring retrovirus-mediated transgene against tumors (80); delivering adenovirus-mediated tumor necrosis factor genes inducing apoptosis (79, 81); carrying oncolytic herpes simplex viruses (82), and so forth.

The aspect common to all the aforementioned potential mechanisms is the intrinsic homing property of specific types of stem cells toward the neural tissue (83). The homing also involves the great aptitude of these cells to migrate into the 'niches' of the tumor, which are the sites where the tumor stem cells reside, giving rise to recurrences both in malignant gliomas and in other CNS tumors (22, 84-86). The homing property regards particularly the h-NSCs and h-MSCs, which have been, not by chance, the most studied lineages in this sense. From a molecular standpoint, the most known pathway at the base of stem cell homing is the complex CXCR4 receptor-stromal cell-derived factor 1 ligand (CXCL12), which is coupled with a G-protein (87). Typically, this complex is expressed at a high level at sites known for their neurogenesis, namely, the subventricular zone, olfactory bulb and the hippocampus. In the mouse brain, the pattern of migration of the therapeutic stem cells toward the tumor site has been reported to be similar to that of h-NSCs (77, 88). Further mediators of cellular migration, through the interaction with specific receptors, are the stem cell factor, the platelet-derived growth factor BB, and the vascular endothelial growth factor (VEGF) (89). In particular, quantitative and qualitative variations of the VEGF and interactions with chemotactic factors Ang2 and GRO $\alpha$  have been associated with the tropism of h-NSCs, but also affect a wide range of vascular pathologies of the CNS (90-92). In regard to h-MSCs, the complex macrophage

migration inhibitory factor-CXCR4 has been recently reported to be among the main pathways in migration and homing in this specific population of stem cells (93). Even h-iPSCs are thought to hold chemotactic properties toward the glioma cells, although with mechanisms that are still largely unknown (94). For all of these types of cells, the migration property is significantly conditioned by the tumoral microenvironment (95). The selectivity of the stem cells, acting as organic delivery vehicles toward the tumor, is paramount for overcoming the immune tolerance and immune escape of conventional chemotherapy, and has even been brought into play for pathologies other than CNS tumors (96-98). Once inside the tumor, stem cells can deliver toxins, anti-proliferative drugs, pro-apoptotic, anti-angiogenetic and immunomodulating agents, prodrug activators, nanoparticles and also viral vectors, the last two with the goal of infecting and killing the neoplastic cells (99). These approaches may also be combined with one another or used with conventional chemotherapy in order to enhance the overall effectiveness of the stem-cell therapies. The route of administration of the therapeutic stem cell is a concern in the management of these therapies. In localized brain tumors that underwent surgical gross total resection, the residual tumor cavity may be considered as an elective site for direct release of these drugs. Conversely, diffused, bilateral or advanced CNS tumors present more challenges in their treatment, and the possible routes of administration can be stereotactic or endoscopic. Endoscopy in particular is the means by which the stem cell is delivered into the ventricular cavity, with this technique being moreover considered as something new in addition to the known advantages coming from this minimal invasive approach for other neurological and neurosurgical pathologies (100, 101).

The results of the present study have highlighted, however, that the near totality of the evidence arises from in-vitro or in-vivo data on animals, therefore, they have to be considered as being part of a still pre-clinical phase. None of the reported trials have been, at the current time, conclusive about the effectiveness and safety of the stem cell-based neoadjuvant therapy for brain tumors. Even today, several factors limit the use of stem cells in the current therapeutic protocol of CNS tumors, with these aspects representing, at the

same time, the major challenges of the stem cell-based therapies. A primary factor to be considered is their availability, which is undoubtedly higher for h-MSCs and h-iPSCs, when compared to h-NSCs, for the reason that a precious source of h-iPSCs is the adipose tissue. The same concepts can be extended also to the numerous ethical issues affecting mainly the h-NSCs, and affecting the h-MSCs and h-iPSCs to a lesser extent. The theoretical possibility of a xenogeneic source of stem cells should be considered as a further possible solution to most of these issues in the future. With the advent of the i-PSC, a large part of the problem regarding the use of stem cells has been partially solved, and significant steps forward have been taken in the context of the translational field. Nevertheless, it must be stressed that the therapeutic capability of this specific cell population is still uncertain.

A further issue of no less importance is that of the oncogenicity related to the grafted stem cell, about which several shadows still do exist. Not surprisingly, non-immortalization techniques are generally considered safer than immortalization ones, even though also this assumption requires further evidence.

## Conclusion

The current approach related to the implementation of the stem cell-based therapies in neuro-oncology mainly involves the use of multipotent stem cells, having the h-iPSCs has, however, aroused interest because of their theoretically unlimited availability.

There has been much more testing on h-MSCs and h-NSCs compared to other types of cells, due to a high tropism toward malignant CNS tumor niches.

The possible approaches to CNS malignancies involving the stem cells are numerous, ranging between the inhibition of the spreading of the neoplastic cells and the carrying of oncolytic viruses.

Almost the entire volume of evidence about the effectiveness and safety of the stem cell therapies in neuro-oncology is still at a preclinical level.

The availability, delivery route and oncogenicity, along with the ethical issues, constitute the main challenges related to the use of stem cells in neuro-oncology.

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## Disclosure - Conflict of Interest

Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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