Acta Biomed 2020; Vol. 91, Supplement 7: 51-60 DOI: 10.23750/abm.v91i7-S.9955

Original article

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

Sabino Luzzi[1,2], Alice Giotta Lucifero[1], Ilaria Brambilla[3], Chiara Trabatti[3], Mario Mosconi[4], Salvatore Savasta[3], Thomas Foiadelli[3]

[1] Neurosurgery Unit, Department of Clinical-Surgical, Diagnostic and Pediatric Sciences, University of Pavia, Pavia, Italy; [2] Neurosurgery Unit, Department of Surgical Sciences, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; [3] Pediatric Clinic, Department of Pediatrics, Fondazione IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy; [4] Orthopaedic and Traumatology Unit, Department of Clinical-Surgical, Diagnostic and Pediatric Sciences, University of Pavia, Pavia, Italy

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)

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

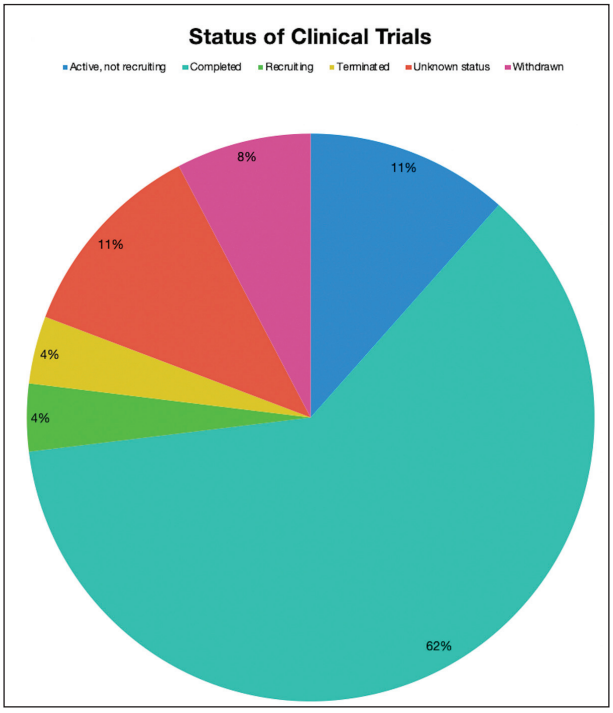
Stem cells may also be classified according to their plasticity. This systematization entails the distinction between totipotent, pluripotent or multipotent cells.

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 lineages (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.

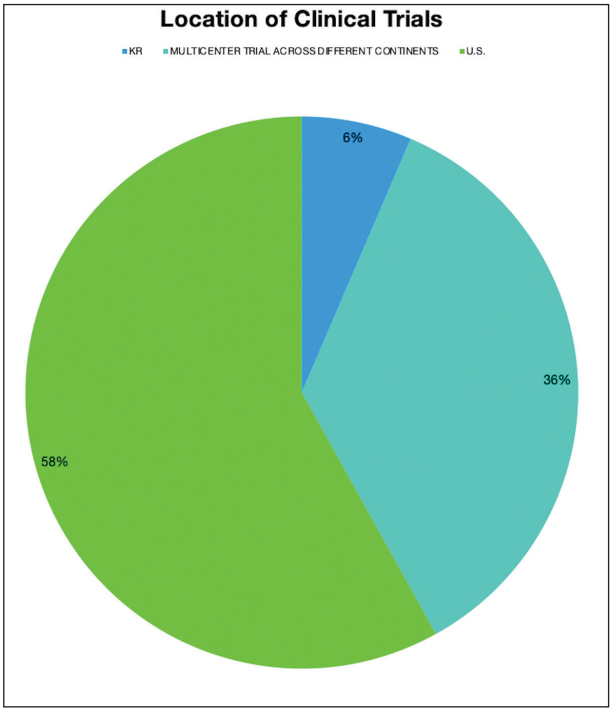
3. Evidence on the Effectiveness and Safety in Neuro-oncology

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.

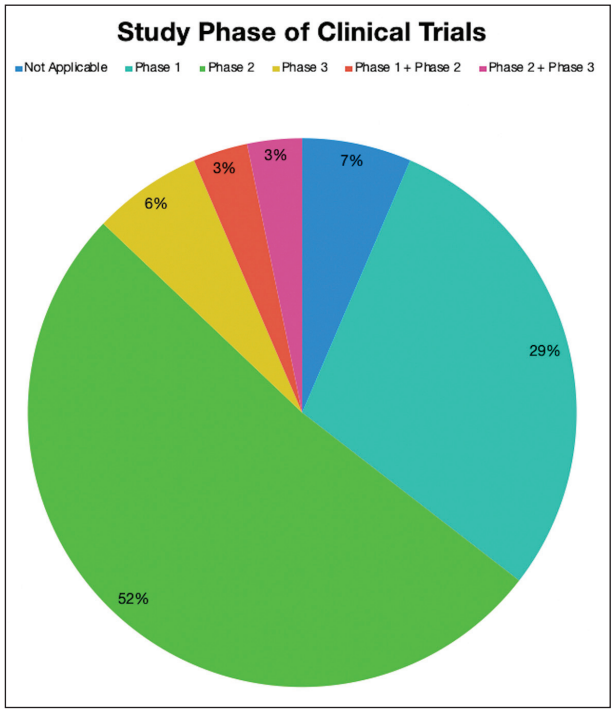
Most of the evidence about the effectiveness of the h-NSCs-based therapy, however, belongs to a preclinical level (65-74). Apart from h-NSCs, h-MSCs also have been widely tested for their potential use in



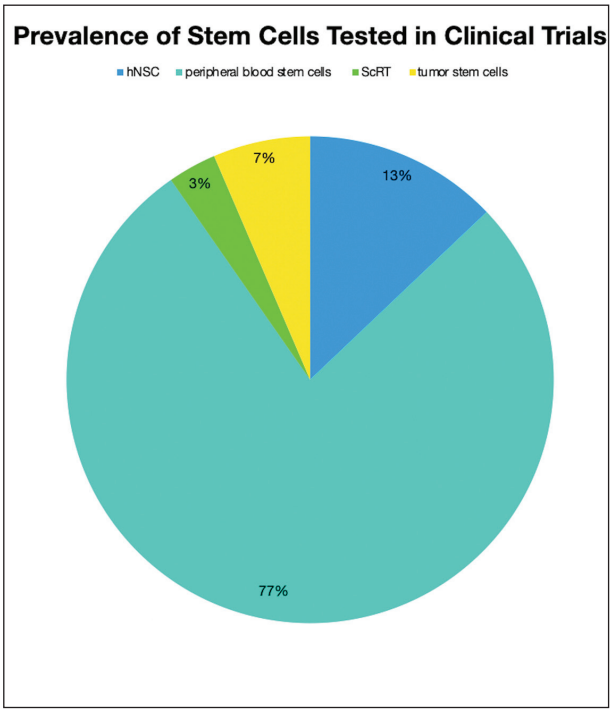
Graph 1. Pie graph showing the distribution of the clinical trials according to the status



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 GROα 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 preclinical 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.

Acknowledgements

We want to thank Giorgia Di Giusto, Engineer, for her invaluable technical support during data collection and analysis.

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.

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

References

1. de Castro F. Cajal and the Spanish Neurological School: Neuroscience Would Have Been a Different Story Without Them. Front Cell Neurosci. 2019;13: 187. https://doi.org/10.3389/fncel.2019.00187.
2. De Carlos JA, Pedraza M. Santiago Ramon y Cajal: The Cajal Institute and the Spanish Histological School. Anat Rec (Hoboken). 2014;297(10): 1785-1802. https://doi.org/10.1002/ar.23019.
3. Berciano J, Lafarga M, Berciano M. Santiago Ramon y Cajal. Neurologia. 2001;16(3): 118-121.
4. Pascual-Castroviejo I, Lopez-Pereira P, Savasta S, Lopez-Gutierrez JC, Lago CM, Cisternino M. Neurofibromatosis type 1 with external genitalia involvement presentation of 4 patients. J Pediatr Surg. 2008;43(11): 1998-2003. https://doi.org/10.1016/j.jpedsurg.2008.01.074.
5. Savasta S, Chiapedi S, Perrini S, Tognato E, Corsano L, Chiara A. Pai syndrome: a further report of a case with bifid nose, lipoma, and agenesis of the corpus callosum. Childs Nerv Syst. 2008;24(6): 773-776. https://doi.org/10.1007/s00381-008-0613-9.
6. Parisi P, Vanacore N, Belcastro V, et al. Clinical guidelines in pediatric headache: evaluation of quality using the AGREE II instrument. J Headache Pain. 2014;15: 57. https://doi.org/10.1186/1129-2377-15-57.
7. Salpietro V, Mankad K, Kinali M, et al. Pediatric idiopathic intracranial hypertension and the underlying endocrine-metabolic dysfunction: a pilot study. J Pediatr Endocrinol Metab. 2014;27(1-2): 107-115. https://doi.org/10.1515/jpem-2013-0156.
8. Foiadelli T, Piccorossi A, Sacchi L, et al. Clinical characteristics of headache in Italian adolescents aged 11-16 years: a

cross-sectional questionnaire school-based study. Ital J Pediatr. 2018;44(1): 44. https://doi.org/10.1186/s13052-018-0486-9.
9. Garone G, Reale A, Vanacore N, et al. Acute ataxia in paediatric emergency departments: a multicentre Italian study. Arch Dis Child. 2019;104(8): 768-774. https://doi.org/10.1136/archdischild-2018-315487.
10. Nosadini M, Granata T, Matricardi S, et al. Relapse risk factors in anti-N-methyl-D-aspartate receptor encephalitis. Dev Med Child Neurol. 2019;61(9): 1101-1107. https://doi.org/10.1111/dmcn.14267.
11. Shyh-Chang N, Ng HH. The metabolic programming of stem cells. Genes Dev. 2017;31(4): 336-346. https://doi.org/10.1101/gad.293167.116.
12. Laplane L, Solary E. Towards a classification of stem cells. Elife. 2019;8. https://doi.org/10.7554/eLife.46563.
13. Challenging Stem Cells. Cell. 2018;173(5): 1063-1065. https://doi.org/10.1016/j.cell.2018.05.010.
14. Pourquié O. Human embryonic stem cells get organized. Nature. 2018;558(7708): 35-36. https://doi.org/10.1038/d41586-018-05115-y.
15. Baumann K. Stem cells: A key to totipotency. Nat Rev Mol Cell Biol. 2017;18(3): 137. https://doi.org/10.1038/nrm.2017.9.
16. Vivanco Mdel M. Mammary Stem Cells. Preface. Methods Mol Biol. 2015;1293: v-vi. https://doi.org/10.1007/978-1-4939-2519-3.
17. Kawasaki T, Yu RK. Special issue: Glycobiology on stem cells ---editorial. Glycoconj J. 2017;34(6): 691. https://doi.org/10.1007/s10719-017-9803-6.
18. Zheng L. Editorial: Epigenetic Regulation on Stem Cells Fate and Regeneration. Curr Stem Cell Res Ther. 2018;13(1): 3. https://doi.org/10.2174/1574888x1301171227105835.
19. Wrighton KH. Stem cells: The different flavours of iPS cells. Nat Rev Genet. 2017;18(7): 394. https://doi.org/10.1038/nrg.2017.42.
20. Maraldi T, Angeloni C, Giannoni E, Sell C. Reactive Oxygen Species in Stem Cells. Oxid Med Cell Longev. 2015;2015: 159080. https://doi.org/10.1155/2015/159080.
21. Yamashita YM. Cell biology of stem cells: studying stem cells at the level of cell biology and studying cell biology using stem cells. Mol Biol Cell. 2018;29(24): 2912. https://doi.org/10.1091/mbc.E18-09-0596.
22. Luzzi S, Crovace AM, Del Maestro M, et al. The cell-based approach in neurosurgery: ongoing trends and future perspectives. Heliyon. 2019;5(11). https://doi.org/10.1016/j.heliyon.2019.e02818.
23. Damdimopoulou P, Rodin S, Stenfelt S, Antonsson L, Tryggvason K, Hovatta O. Human embryonic stem cells. Best Pract Res Clin Obstet Gynaecol. 2016;31: 2-12. https://doi.org/10.1016/j.bpobgyn.2015.08.010.
24. Lerou P. Embryonic stem cell derivation from human embryos. Methods Mol Biol. 2011;767: 31-35. https://doi.org/10.1007/978-1-61779-201-4_3.
25. Ilic D, Ogilvie C. Concise Review: Human Embryonic Stem Cells-What Have We Done? What Are We Doing? Where Are We Going? Stem Cells. 2017;35(1): 17-25. https://doi.org/10.1002/stem.2450.
26. Itskovitz-Eldor J. 20th Anniversary of Isolation of Human Embryonic Stem Cells: A Personal Perspective. Stem Cell Reports. 2018;10(5): 1439-1441. https://doi.org/10.1016/j.stemcr.2018.04.011.
27. Crook JM, Kravets L, Peura T, Firpo MT. Derivation of Human Embryonic Stem Cells. Methods Mol Biol. 2017;1590: 115-129. https://doi.org/10.1007/978-1-4939-6921-0_8.
28. Andrews PW. From teratocarcinomas to embryonic stem cells. Philos Trans R Soc Lond B Biol Sci. 2002;357(1420): 405-417. https://doi.org/10.1098/rstb.2002.1058.
29. Bonner AE, Wang Y, You M. Gene expression profiling of mouse teratocarcinomas uncovers epigenetic changes associated with the transformation of mouse embryonic stem cells. Neoplasia. 2004;6(5): 490-502. https://doi.org/10.1593/neo.04124.
30. Chambers I, Smith A. Self-renewal of teratocarcinoma and embryonic stem cells. Oncogene. 2004;23(43): 7150-7160. https://doi.org/10.1038/sj.onc.1207930.
31. Weiss ML, Medicetty S, Bledsoe AR, et al. Human umbilical cord matrix stem cells: preliminary characterization and effect of transplantation in a rodent model of Parkinson's disease. Stem Cells. 2006;24(3): 781-792. https://doi.org/10.1634/stemcells.2005-0330.
32. Weiss ML, Anderson C, Medicetty S, et al. Immune properties of human umbilical cord Wharton's jelly-derived cells. Stem Cells. 2008;26(11): 2865-2874. https://doi.org/10.1634/stemcells.2007-1028.
33. Weiss ML, Troyer DL. Stem cells in the umbilical cord. Stem Cell Rev. 2006;2(2): 155-162. https://doi.org/10.1007/s12015-006-0022-y.
34. Li T, Xia M, Gao Y, Chen Y, Xu Y. Human umbilical cord mesenchymal stem cells: an overview of their potential in cell-based therapy. Expert Opin Biol Ther. 2015;15(9): 1293-1306. https://doi.org/10.1517/14712598.2015.1051528.
35. El Omar R, Beroud J, Stoltz JF, Menu P, Velot E, Decot V. Umbilical cord mesenchymal stem cells: the new gold standard for mesenchymal stem cell-based therapies? Tissue Eng Part B Rev. 2014;20(5): 523-544. https://doi.org/10.1089/ten.TEB.2013.0664.
36. Ding DC, Chang YH, Shyu WC, Lin SZ. Human umbilical cord mesenchymal stem cells: a new era for stem cell therapy. Cell Transplant. 2015;24(3): 339-347. https://doi.org/10.3727/096368915x686841.
37. Clevers H. STEM CELLS. What is an adult stem cell? Science. 2015;350(6266): 1319-1320. https://doi.org/10.1126/science.aad7016.
38. Prentice DA. Adult Stem Cells. Circ Res. 2019;124(6): 837-839. https://doi.org/10.1161/circresaha.118.313664.
39. Dulak J, Szade K, Szade A, Nowak W, Józkowicz A. Adult stem cells: hopes and hypes of regenerative medicine. Acta Biochim Pol. 2015;62(3): 329-337. https://doi.org/10.18388/abp.2015_1023.
40. Clevers H, Watt FM. Defining Adult Stem Cells by Func-

tion, not by Phenotype. Annu Rev Biochem. 2018;87: 1015-1027. https://doi.org/10.1146/annurev-biochem-062917-012341.
41. Crane GM, Jeffery E, Morrison SJ. Adult haematopoietic stem cell niches. Nat Rev Immunol. 2017;17(9): 573-590. https://doi.org/10.1038/nri.2017.53.
42. Gonçalves JT, Schafer ST, Gage FH. Adult Neurogenesis in the Hippocampus: From Stem Cells to Behavior. Cell. 2016;167(4): 897-914. https://doi.org/10.1016/j.cell.2016.10.021.
43. Kriegstein A, Alvarez-Buylla A. The glial nature of embryonic and adult neural stem cells. Annu Rev Neurosci. 2009;32: 149-184. https://doi.org/10.1146/annurev.neuro.051508.135600.
44. Zupanc GKH, Monaghan JR, Stocum DL. Adult Neural Stem Cells in Development, Regeneration, and Aging. Dev Neurobiol. 2019;79(5): 391-395. https://doi.org/10.1002/dneu.22702.
45. Sanberg PR, Eve DJ, Metcalf C, Borlongan CV. Advantages and challenges of alternative sources of adult-derived stem cells for brain repair in stroke. Prog Brain Res. 2012;201: 99-117. https://doi.org/10.1016/b978-0-444-59544-7.00006-8.
46. Macrin D, Joseph JP, Pillai AA, Devi A. Eminent Sources of Adult Mesenchymal Stem Cells and Their Therapeutic Imminence. Stem Cell Rev Rep. 2017;13(6): 741-756. https://doi.org/10.1007/s12015-017-9759-8.
47. Baker CL, Pera MF. Capturing Totipotent Stem Cells. Cell Stem Cell. 2018;22(1): 25-34. https://doi.org/10.1016/j.stem.2017.12.011.
48. Hayashi Y, Ohnuma K, Furue MK. Pluripotent Stem Cell Heterogeneity. Adv Exp Med Biol. 2019;1123: 71-94. https://doi.org/10.1007/978-3-030-11096-3_6.
49. Sobhani A, Khanlarkhani N, Baazm M, et al. Multipotent Stem Cell and Current Application. Acta Med Iran. 2017;55(1): 6-23.
50. Kempermann G, Song H, Gage FH. Neurogenesis in the Adult Hippocampus. Cold Spring Harb Perspect Biol. 2015;7(9): a018812. https://doi.org/10.1101/cshperspect.a018812.
51. Lim DA, Alvarez-Buylla A. The Adult Ventricular-Subventricular Zone (V-SVZ) and Olfactory Bulb (OB) Neurogenesis. Cold Spring Harb Perspect Biol. 2016;8(5). https://doi.org/10.1101/cshperspect.a018820.
52. McKay R. Stem cells in the central nervous system. Science. 1997;276(5309): 66-71. https://doi.org/10.1126/science.276.5309.66.
53. Daniela F, Vescovi AL, Bottai D. The stem cells as a potential treatment for neurodegeneration. Methods Mol Biol. 2007;399: 199-213. https://doi.org/10.1007/978-1-59745-504-6_14.
54. Ourednik V, Ourednik J, Park KI, Snyder EY. Neural stem cells -- a versatile tool for cell replacement and gene therapy in the central nervous system. Clin Genet. 1999;56(4): 267-278. https://doi.org/10.1034/j.1399-0004.1999.560403.x.
55. Zheng T, Marshall Ii GP, 2nd, Chen KA, Laywell ED. Transplantation of neural stem/progenitor cells into developing and adult CNS. Methods Mol Biol. 2009;482: 185-197. https://doi.org/10.1007/978-1-59745-060-7_12.
56. Dietrich J, Kempermann G. Role of endogenous neural stem cells in neurological disease and brain repair. Adv Exp Med Biol. 2006;557: 191-220. https://doi.org/10.1007/0-387-30128-3_12.
57. Sharp J, Keirstead HS. Stem cell-based cell replacement strategies for the central nervous system. Neurosci Lett. 2009;456(3): 107-111. https://doi.org/10.1016/j.neulet.2008.04.106.
58. Armstrong RJ, Svendsen CN. Neural stem cells: from cell biology to cell replacement. Cell Transplant. 2000;9(2): 139-152. https://doi.org/10.1177/096368970000900202.
59. Frisén J, Johansson CB, Lothian C, Lendahl U. Central nervous system stem cells in the embryo and adult. Cell Mol Life Sci. 1998;54(9): 935-945. https://doi.org/10.1007/s000180050224.
60. Trujillo CA, Schwindt TT, Martins AH, Alves JM, Mello LE, Ulrich H. Novel perspectives of neural stem cell differentiation: from neurotransmitters to therapeutics. Cytometry A. 2009;75(1): 38-53. https://doi.org/10.1002/cyto.a.20666.
61. Zhang J, Jiao J. Molecular Biomarkers for Embryonic and Adult Neural Stem Cell and Neurogenesis. Biomed Res Int. 2015;2015: 727542. https://doi.org/10.1155/2015/727542.
62. Yu J, Vodyanik MA, Smuga-Otto K, et al. Induced pluripotent stem cell lines derived from human somatic cells. Science. 2007;318(5858): 1917-1920. https://doi.org/10.1126/science.1151526.
63. Takahashi K, Tanabe K, Ohnuki M, et al. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell. 2007;131(5): 861-872. https://doi.org/10.1016/j.cell.2007.11.019.
64. Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell. 2006;126(4): 663-676. https://doi.org/10.1016/j.cell.2006.07.024.
65. Tobias AL, Thaci B, Auffinger B, et al. The timing of neural stem cell-based virotherapy is critical for optimal therapeutic efficacy when applied with radiation and chemotherapy for the treatment of glioblastoma. Stem Cells Transl Med. 2013;2(9): 655-666. https://doi.org/10.5966/sctm.2013-0039.
66. Ahmed AU, Thaci B, Tobias AL, et al. A preclinical evaluation of neural stem cell-based cell carrier for targeted antiglioma oncolytic virotherapy. J Natl Cancer Inst. 2013;105(13): 968-977. https://doi.org/10.1093/jnci/djt141.
67. Ahmed AU, Tyler MA, Thaci B, et al. A comparative study of neural and mesenchymal stem cell-based carriers for oncolytic adenovirus in a model of malignant glioma. Mol Pharm. 2011;8(5): 1559-1572. https://doi.org/10.1021/mp200161f.
68. Ahmed AU, Thaci B, Alexiades NG, et al. Neural stem cell-based cell carriers enhance therapeutic efficacy of an oncolytic adenovirus in an orthotopic mouse model of human

glioblastoma. Mol Ther. 2011;19(9): 1714-1726. https://doi.org/10.1038/mt.2011.100.
69. Ulasov IV, Sonabend AM, Nandi S, Khramtsov A, Han Y, Lesniak MS. Combination of adenoviral virotherapy and temozolomide chemotherapy eradicates malignant glioma through autophagic and apoptotic cell death in vivo. Br J Cancer. 2009;100(7): 1154-1164. https://doi.org/10.1038/sj.bjc.6604969.
70. Nandi S, Ulasov IV, Tyler MA, et al. Low-dose radiation enhances survivin-mediated virotherapy against malignant glioma stem cells. Cancer Res. 2008;68(14): 5778-5784. https://doi.org/10.1158/0008-5472.Can-07-6441.
71. Ulasov IV, Zhu ZB, Tyler MA, et al. Survivin-driven and fiber-modified oncolytic adenovirus exhibits potent antitumor activity in established intracranial glioma. Hum Gene Ther. 2007;18(7): 589-602. https://doi.org/10.1089/hum.2007.002.
72. Mutukula N, Elkabetz Y. "Neural Killer" Cells: Autologous Cytotoxic Neural Stem Cells for Fighting Glioma. Cell Stem Cell. 2017;20(4): 426-428. https://doi.org/10.1016/j.stem.2017.03.019.
73. Bagó JR, Okolie O, Dumitru R, et al. Tumor-homing cytotoxic human induced neural stem cells for cancer therapy. Sci Transl Med. 2017;9(375). https://doi.org/10.1126/scitranslmed.aah6510.
74. Bagó JR, Sheets KT, Hingtgen SD. Neural stem cell therapy for cancer. Methods. 2016;99: 37-43. https://doi.org/10.1016/j.ymeth.2015.08.013.
75. Vieira de Castro J, Gomes ED, Granja S, et al. Impact of mesenchymal stem cells' secretome on glioblastoma pathophysiology. J Transl Med. 2017;15(1): 200. https://doi.org/10.1186/s12967-017-1303-8.
76. Gomes ED, Vieira de Castro J, Costa BM, Salgado AJ. The impact of Mesenchymal Stem Cells and their secretome as a treatment for gliomas. Biochimie. 2018;155: 59-66. https://doi.org/10.1016/j.biochi.2018.07.008.
77. Aboody KS, Brown A, Rainov NG, et al. Neural stem cells display extensive tropism for pathology in adult brain: evidence from intracranial gliomas. Proc Natl Acad Sci U S A. 2000;97(23): 12846-12851. https://doi.org/10.1073/pnas.97.23.12846.
78. Brown AB, Yang W, Schmidt NO, et al. Intravascular delivery of neural stem cell lines to target intracranial and extracranial tumors of neural and non-neural origin. Hum Gene Ther. 2003;14(18): 1777-1785. https://doi.org/10.1089/104303403322611782.
79. Oh MC, Lim DA. Novel treatment strategies for malignant gliomas using neural stem cells. Neurotherapeutics. 2009;6(3): 458-464. https://doi.org/10.1016/j.nurt.2009.05.003.
80. Kim SK, Kim SU, Park IH, et al. Human neural stem cells target experimental intracranial medulloblastoma and deliver a therapeutic gene leading to tumor regression. Clin Cancer Res. 2006;12(18): 5550-5556. https://doi.org/10.1158/1078-0432.Ccr-05-2508.
81. Yang B, Wu X, Mao Y, et al. Dual-targeted antitumor effects against brainstem glioma by intravenous delivery of tumor necrosis factor-related, apoptosis-inducing, ligand-engineered human mesenchymal stem cells. Neurosurgery. 2009;65(3): 610-624; discussion 624. https://doi.org/10.1227/01.Neu.0000350227.61132.A7.
82. Du W, Seah I, Bougazzoul O, et al. Stem cell-released oncolytic herpes simplex virus has therapeutic efficacy in brain metastatic melanomas. Proc Natl Acad Sci U S A. 2017;114(30): E6157-e6165. https://doi.org/10.1073/pnas.1700363114.
83. Shah K, Hingtgen S, Kasmieh R, et al. Bimodal viral vectors and in vivo imaging reveal the fate of human neural stem cells in experimental glioma model. J Neurosci. 2008;28(17): 4406-4413. https://doi.org/10.1523/jneurosci.0296-08.2008.
84. Cheng CY, Shetty R, Sekhar LN. Microsurgical Resection of a Large Intraventricular Trigonal Tumor: 3-Dimensional Operative Video. Oper Neurosurg (Hagerstown). 2018;15(6): E92-E93. https://doi.org/10.1093/ons/opy068.
85. Palumbo P, Lombardi F, Siragusa G, et al. Involvement of NOS2 Activity on Human Glioma Cell Growth, Clonogenic Potential, and Neurosphere Generation. Int J Mol Sci. 2018;19(9). https://doi.org/10.3390/ijms19092801.
86. Bellantoni G, Guerrini F, Del Maestro M, Galzio R, Luzzi S. Simple schwannomatosis or an incomplete Coffin-Siris? Report of a particular case. eNeurologicalSci. 2019;14: 31-33. https://doi.org/10.1016/j.ensci.2018.11.021.
87. Tran PB, Banisadr G, Ren D, Chenn A, Miller RJ. Chemokine receptor expression by neural progenitor cells in neurogenic regions of mouse brain. J Comp Neurol. 2007;500(6): 1007-1033. https://doi.org/10.1002/cne.21229.
88. Tang Y, Shah K, Messerli SM, Snyder E, Breakefield X, Weissleder R. In vivo tracking of neural progenitor cell migration to glioblastomas. Hum Gene Ther. 2003;14(13): 1247-1254. https://doi.org/10.1089/104303403767740786.
89. Koizumi S, Gu C, Amano S, et al. Migration of mouse-induced pluripotent stem cells to glioma-conditioned medium is mediated by tumor-associated specific growth factors. Oncol Lett. 2011;2(2): 283-288. https://doi.org/10.3892/ol.2011.234.
90. Ricci A, Di Vitantonio H, De Paulis D, et al. Cortical aneurysms of the middle cerebral artery: A review of the literature. Surg Neurol Int. 2017;8: 117. https://doi.org/10.4103/sni.sni_50_17.
91. Luzzi S, Elia A, Del Maestro M, et al. Indication, Timing, and Surgical Treatment of Spontaneous Intracerebral Hemorrhage: Systematic Review and Proposal of a Management Algorithm. World Neurosurg. 2019. https://doi.org/10.1016/j.wneu.2019.01.016.
92. Schmidt NO, Koeder D, Messing M, et al. Vascular endothelial growth factor-stimulated cerebral microvascular endothelial cells mediate the recruitment of neural stem cells to the neurovascular niche. Brain Res. 2009;1268: 24-37. https://doi.org/10.1016/j.brainres.2009.02.065.
93. Lourenco S, Teixeira VH, Kalber T, Jose RJ, Floto RA, Janes

SM. Macrophage migration inhibitory factor-CXCR4 is the dominant chemotactic axis in human mesenchymal stem cell recruitment to tumors. J Immunol. 2015;194(7): 3463-3474. https://doi.org/10.4049/jimmunol.1402097.
94. Yamazoe T, Koizumi S, Yamasaki T, Amano S, Tokuyama T, Namba H. Potent tumor tropism of induced pluripotent stem cells and induced pluripotent stem cell-derived neural stem cells in the mouse intracerebral glioma model. Int J Oncol. 2015;46(1): 147-152. https://doi.org/10.3892/ijo.2014.2702.
95. Stuckey DW, Shah K. Stem cell-based therapies for cancer treatment: separating hope from hype. Nat Rev Cancer. 2014;14(10): 683-691. https://doi.org/10.1038/nrc3798.
96. Millimaggi DF, Norcia VD, Luzzi S, Alfiero T, Galzio RJ, Ricci A. Minimally Invasive Transforaminal Lumbar Interbody Fusion with Percutaneous Bilateral Pedicle Screw Fixation for Lumbosacral Spine Degenerative Diseases. A Retrospective Database of 40 Consecutive Cases and Literature Review. Turk Neurosurg. 2018;28(3): 454-461. https://doi.org/10.5137/1019-5149.JTN.19479-16.0.
97. Rolfe A, Sun D. Stem Cell Therapy in Brain Trauma: Implications for Repair and Regeneration of Injured Brain in Experimental TBI Models. CRC Press/Taylor & Francis, Boca Raton (FL); 2015.
98. Zoia C, Bongetta D, Dorelli G, Luzzi S, Maestro MD, Galzio RJ. Transnasal endoscopic removal of a retrochiasmatic cavernoma: A case report and review of literature. Surg Neurol Int. 2019;10: 76. https://doi.org/10.25259/SNI-132-2019.
99. Shah K. Stem cell-based therapies for tumors in the brain: are we there yet? Neuro Oncol. 2016;18(8): 1066-1078. https://doi.org/10.1093/neuonc/now096.
100. Luzzi S, Del Maestro M, Elia A, et al. Morphometric and Radiomorphometric Study of the Correlation Between the Foramen Magnum Region and the Anterior and Posterolateral Approaches to Ventral Intradural Lesions. Turk Neurosurg. 2019. https://doi.org/10.5137/1019-5149.JTN.26052-19.2.
101. Luzzi S, Zoia C, Rampini AD, et al. Lateral Transorbital Neuroendoscopic Approach for Intraconal Meningioma of the Orbital Apex: Technical Nuances and Literature Review. World Neurosurg. 2019;131: 10-17. https://doi.org/10.1016/j.wneu.2019.07.152.

Received: 10 May 2020
Accepted: 1 June 2020
Correspondence:
Sabino Luzzi M.D., Ph.D.
Neurosurgery Unit, Department of Clinical-Surgical, Diagnostic and Pediatric Sciences, University of Pavia
Polo Didattico "Cesare Brusotti", Viale Brambilla, 74
27100 - Pavia (Italy)
E-mail: sabino.luzzi@unipv.it

Appendix

SUPPLEMENTARY FILE: Table 1
Clinical Trials on Stem Cells Therapies for Malignant Central Nervous System Tumors

Rank	ClinicalTrials.gov Identifier NCT Number	Title	Status	Study Results	Conditions	Interventions	Type of Stem Cells	Study Phase	# of Pts. Estimated Enrollment
1	NCT04072134	Neural Stem Cell Based Viroltherapy of Newly Diagnosed Malignant Glioma	Recruiting	No Results Available	Glioma|Anaplastic Astrocytoma|Anaplastic Oligodendroglioma|Anaplastic Oligoastrocytoma|Glioblastoma Multiforme|Astrocytoma, Grade III|Astrocytoma, Grade IV|Brain Cancer	Biological: Neural stem cells loaded with an oncolytic adenovirus	hNSCs	Phase 1	36
2	NCT02055196	Genetically Modified Stem Cells and Irinotecan Hydrochloride in Treating Patients With Recurrent High-Grade Gliomas	Withdrawn	No Results Available	Adult Anaplastic Astrocytoma|Adult Anaplastic Oligodendroglioma|Adult Giant Cell Glioblastoma|Adult Glioblastoma|Adult Gliosarcoma|Recurrent Adult Brain Tumor	Biological: carboxylesterase-expressing allogeneic neural stem cells|Drug: irinotecan hydrochloride|Other: laboratory biomarker analysis	hNSCs	Phase 1	0
3	NCT02039778	Stem Cell Radiotherapy and Temozolomide for Newly Diagnosed High-grade Glioma	Terminated	Has Results	Glioblastoma|Malignant Glioma|Brain Tumor|Anaplastic Astrocytoma	Radiation: Stem Cell Radiotherapy (SciRT) and Temozolomide	SciRT	Not Applicable	4
4	NCT02015819	Genetically Modified Neural Stem Cells, Flucytosine, and Leucovorin for Treating Patients With Recurrent High-Grade Gliomas	Active, not recruiting	No Results Available	Adult Anaplastic Astrocytoma|Adult Anaplastic Oligodendroglioma|Adult Giant Cell Glioblastoma|Adult Glioblastoma|Adult Gliosarcoma|Recurrent Adult Brain Tumor|Anaplastic Oligoastrocytoma	Biological: E. coli CD-expressing genetically modified neural stem cells|Drug: flucytosine|Drug: leucovorin calcium|Other: pharmacological study|Other: laboratory biomarker analysis	hNSCs	Phase 1	18
5	NCT01342237	Tandem High-Dose Chemotherapy and Autologous Stem Cell Rescue for High Risk Pediatric Brain Tumors	Unknown status	No Results Available	Brain Tumors	Drug: HDCT 1(TTC), HDCT2(MEC)	peripheral blood stem cells	Phase 2	33
6	NCT01172964	A Pilot Feasibility Study of Oral 5-Fluorocytosine and Genetically-Modified Neural Stem Cells Expressing E.Coli Cytosine Deaminase for Treatment of Recurrent High Grade Gliomas	Completed	No Results Available	Adult Anaplastic Astrocytoma|Recurrent Grade III Glioma|Recurrent Grade IV Glioma|Adult Anaplastic Oligodendroglioma|Adult Brain Tumor|Adult Giant Cell Glioblastoma|Adult Glioblastoma|Adult Gliosarcoma|Adult Mixed Glioma|Recurrent Adult Brain Tumor|Adult Anaplastic Oligoastrocytoma|Recurrent High Grade Glioma	Drug: flucytosine: Other: polymerase chain reaction|Other: immunohistochemistry staining method|Biological: gene therapy|Other: pharmacological study|Other: 3-Tesla magnetic resonance imaging|Other: laboratory biomarker analysis|Procedure: therapeutic conventional surgery|Biological: E. coli CD-expressing genetically modified neural stem cells	hNSCs	Phase 1	15
7	NCT01171469	Vaccination With Dendritic Cells Loaded With Brain Tumor Stem Cells for Progressive Malignant Brain Tumor	Completed	No Results Available	Brain Tumor|Glioblastoma|Medulloblastoma|Ependymoma|Anaplastic Astrocytoma	Biological: Dendritic Cells|Drug: Imiquimod	tumor stem cells	Phase 1	8
8	NCT00846456	Safe Study of Dendritic Cell (DC) Based Therapy Targeting Tumor Stem Cells in Glioblastoma	Completed	No Results Available	Glioblastoma|Brain Tumor	Biological: Dendritic cell vaccine with mRNA from tumor stem cells	tumor stem cells	Phase 1|Phase 2	20
9	NCT00778881	High-dose Chemotherapy With Autologous Stem Cell Rescue in Pediatric High-risk Brain Tumors	Active, not recruiting	No Results Available	Brain Tumor	Procedure: high-dose chemotherapy and autologous stem cell rescue	peripheral blood stem cells	Phase 2	100
10	NCT01596154	Rituximab, Methotrexate, Procarbazine and Vincristine Followed by High-dose Chemotherapy With Autologous Stem-cell Rescue in Newly-diagnosed Primary CNS Lymphoma	Active, not recruiting	No Results Available	CNS Lymphoma|CNS Brain Cancer|Non-Hodgkin's Lymphoma	Other: Rituximab, Methotrexate, Vincristine, Procarbazine, PBPC) collection, Busulfan, Thiotepa, and Cyclophosphamide	peripheral blood stem cells	Phase 2	33
11	NCT00528437	Temozolomide, Thotepa and Carboplatin With Autologous Stem Cell Rescue Followed by 13-cis-retinoic Acid in Patients With Recurrent/Refractory Malignant Brain Tumors	Completed	No Results Available	Brain Tumors	Drug: temozolomide, thotepa, carboplatin, 13-cis-retinoic acid	peripheral blood stem cells	Phase 2	46
12	NCT01028286	Combination Chemotherapy With or Without Etoposide Followed By an Autologous Stem Cell Transplant in Treating Young Patients With Previously Untreated Malignant Brain Tumors	Unknown status	No Results Available	Brain and Central Nervous System Tumors	Drug: carboplatin|Drug: cisplatin|Drug: cyclophosphamide|Drug: etoposide|Drug: methotrexate|Drug: temozolomide|Drug: thiotepa|Drug: vincristine sulfate|Procedure: autologous bone marrow transplantation|Procedure: autologous hematopoietic stem cell	peripheral blood stem cells	Phase 3	120
13	NCT00254787	Combination Chemotherapy and Radiation Therapy in Treating Younger Patients Who Are Undergoing an Autologous Stem Cell Transplant for Newly Diagnosed Gliomas	Completed	No Results Available	Brain and Central Nervous System Tumors	Drug: Ofosfamide|Lomustine|Drug: busulfan|Drug: temozolomide|Procedure: adjuvant therapy|Procedure: autologous bone marrow transplantation|Procedure: conventional surgery|Procedure: peripheral blood stem cell transplantation|Radiation: radiation therapy	peripheral blood stem cells	Not Applicable	n/a
14	NCT00176943	Stem Cell Transplant for High Risk Central Nervous System (CNS) Tumors	Unknown status	No Results Available	Glioblastoma|Astrocytoma|Pineoblastoma|Rhabdoid Tumor|Supratentorial Neoplasms	Procedure: Stem Cell Transplant	peripheral blood stem cells	Phase 2|Phase 3	50
15	NCT00005819	Chemotherapy Followed by Bone Marrow or Peripheral Stem Cell Transplantation in Treating Patients With Glioblastoma Multiforme or Brain Stem Tumors	Completed	No Results Available	Brain and Central Nervous System Tumors	Biological: filgrastim|Drug: carboplatin|Drug: thiotepa|Procedure: autologous bone marrow transplantation|Procedure: peripheral blood stem cell transplantation	peripheral blood stem cells	Phase 2	60
16	NCT00003946	Radiation Therapy, Chemotherapy, and Peripheral Stem Cell Transplantation in Treating Patients With Primitive Neuroectodermal Tumors	Completed	No Results Available	Brain and Central Nervous System Tumors|Neuroblastoma	Biological: filgrastim|Drug: carboplatin|Drug: cyclophosphamide|Drug: thiotepa|Drug: vincristine sulfate|Procedure: bone marrow ablation with stem cell support|Procedure: peripheral blood stem cell transplantation|Radiation: radiation therapy	peripheral blood stem cells	Phase 2	25
17	NCT00003101	Combination Chemotherapy and Bone Marrow Transplantation or Peripheral Stem Cell Transplantation in Treating Patients With Oligodendrogliomas	Completed	No Results Available	Brain and Central Nervous System Tumors	Biological: filgrastim|Drug: busulfan|Drug: lomustine|Drug: procarbazine hydrochloride|Drug: thiotepa|Drug: vincristine sulfate|Procedure: autologous bone marrow transplantation|Procedure: peripheral blood stem cell transplantation	peripheral blood stem cells	Phase 2	60
18	NCT00005796	Combination Chemotherapy Plus Gene Therapy in Treating Patients With CNS Tumors	Completed	No Results Available	Bone Marrow Suppression|Brain and Central Nervous System Tumors|Drug/Agent Toxicity by Tissue/Organ	Procedure: filgrastim|Biological: gene therapy|Drug: lomustine|Drug: procarbazine hydrochloride|Drug: vincristine sulfate|Procedure: in vitro-treated peripheral blood stem cell transplantation	peripheral blood stem cells	Phase 1	10
19	NCT00014573	Chemotherapy and Vaccine Therapy Followed by Bone Marrow or Peripheral Stem Cell Transplantation and Interleukin-2 in Treating Patients With Recurrent or Refractory Brain Cancer	Completed	No Results Available	Brain and Central Nervous System Tumors	Biological: interleukin-2|Biological: sargramostim|Biological: tumor cell vaccine|Biological: filgrastim|Biological: sargramostim|Biological: therapeutic autologous lymphocytes|Drug: sargramostim|Drug: cyclophosphamide|Drug: dacarbazine|Procedure:	peripheral blood stem cells	Phase 2	n/a
20	NCT00007813	Peripheral Stem Cell Transplantation Plus Chemotherapy in Treating Patients With Malignant Solid Tumors	Completed	No Results Available	Brain and Central Nervous System Tumors|Childhood Germ Cell Tumor|Extragonadal Germ Cell Tumor|Liver Cancer|Neuroblastoma|Ovarian Cancer|Sarcoma|Testicular Germ Cell Tumor	Biological: filgrastim|Drug: carboplatin|Drug: cyclophosphamide|Drug: etoposide|Procedure: autologous bone marrow transplantation|Procedure: peripheral blood stem cell transplantation	peripheral blood stem cells	Phase 1	21
21	NCT00070988	High-Dose Chemotherapy Plus Autologous Stem Cell Transplantation Compared With Intermediate-Dose Chemotherapy Plus Autologous Stem Cell Transplantation With or Without Isotretinoin in Treating Young Patients With Recurrent High-Grade Gliomas	Completed	No Results Available	Brain Tumors|Central Nervous System Tumor	Biological: filgrastim|Drug: carboplatin|Drug: etoposide|Drug: isotretinoin|Drug: thiotepa|Procedure: autologous bone marrow transplantation|Procedure: peripheral blood stem cell transplantation	peripheral blood stem cells	Phase 3	1
22	NCT00003141	Chemotherapy Plus Peripheral Stem Cell Transplantation in Treating Infants With Malignant Brain or Spinal Cord Tumors	Completed	No Results Available	Brain Tumors|Central Nervous System Tumors|Neuroblastoma|Sarcoma	Biological: filgrastim|Drug: carboplatin|Drug: cisplatin|Drug: cyclophosphamide|Drug: etoposide|Drug: thiotepa|Drug: vincristine sulfate|Procedure: conventional surgery|Procedure: peripheral blood stem cell transplantation	peripheral blood stem cells	Phase 1	94
23	NCT00003211	Chemotherapy, Radiation Therapy, and Peripheral Stem Cell Transplantation in Treating Children With Newly Diagnosed Medulloblastoma or Supratentorial Primitive Neuroectodermal Tumor	Completed	No Results Available	Brain and Central Nervous System Tumors	Biological: filgrastim|Drug: amifostine trihydrate|Drug: cisplatin|Drug: cyclophosphamide|Drug: vincristine sulfate|Procedure: peripheral blood stem cell transplantation|Radiation: radiation therapy	peripheral blood stem cells	Phase 2	94
24	NCT00007326	Neoadjuvant Chemotherapy With or Without Second-Look Surgery Followed by Radiation Therapy With or Without Peripheral Stem Cell Transplantation in Treating Patients With Intracranial Germ Cell Tumors	Completed	Has Results	Brain Tumor|Central Nervous System Tumors|Childhood Germ Cell Tumor	Drug: carboplatin|Drug: etoposide|Drug: ifosfamide|Drug: thiotepa|Procedure: adjuvant therapy|Procedure: conventional surgery|Procedure: neoadjuvant therapy|Procedure: peripheral blood stem cell transplantation|Radiation: radiation therapy	peripheral blood stem cells	Phase 2	104
25	NCT00025558	Combination Chemotherapy Followed by Peripheral Stem Cell Transplantation or Bone Marrow Transplantation in Treating Patients With Brain Cancer	Completed	No Results Available	Brain and Central Nervous System Tumors	Biological: filgrastim|Drug: carboplatin|Drug: temozolomide|Drug: thiotepa|Procedure: autologous bone marrow transplantation|Procedure: peripheral blood stem cell transplantation	peripheral blood stem cells	Phase 1	n/a
26	NCT00025324	Chemotherapy, Surgery, Radiation Therapy and Bone Marrow or Peripheral Stem Cell Transplantation in Treating Patients With Primary CNS Germ Cell Tumors	Unknown status	No Results Available	Brain and Central Nervous System Tumors	Biological: filgrastim|Drug: carboplatin|Drug: cyclophosphamide|Drug: etoposide|Drug: thiotepa|Procedure: autologous bone marrow transplantation|Procedure: bone marrow ablation with stem cell support|Procedure: conventional surgery|Procedure: peripheral blood stem cell transplantation|Radiation: radiation therapy	peripheral blood stem cells	Phase 2	n/a
27	NCT00025077	Combination Chemotherapy, Surgery or Radiation Therapy, and Peripheral Stem Cell Transplant in Treating Patients With Recurrent Medulloblastoma or Primitive Neuroectodermal and Pineal Tumors	Completed	No Results Available	Brain and Central Nervous System Tumors	Biological: filgrastim|Drug: carboplatin|Drug: cyclophosphamide|Drug: thiotepa|Procedure: conventional surgery|Procedure: peripheral blood stem cell transplantation|Radiation: radiation therapy	peripheral blood stem cells	Phase 2	50
28	NCT00008008	Thiotepa Followed by Peripheral Stem Cell or Bone Marrow Transplant in Treating Patients With Malignant Glioma	Completed	No Results Available	Brain and Central Nervous System Tumors	Biological: filgrastim|Biological: sargramostim|Drug: cyclophosphamide|Drug: thiotepa|Procedure: autologous bone marrow transplantation|Procedure: bone marrow ablation with stem cell support|Procedure: peripheral blood stem cell transplantation	peripheral blood stem cells	Phase 2	40
29	NCT00007962	Chemotherapy Plus Peripheral Stem Cell Transplant in Treating Patients With Central Nervous System Cancer	Completed	No Results Available	Brain and Central Nervous System Tumors|Head and Neck Cancer|Lymphoma	Biological: filgrastim|Drug: carboplatin|Drug: cyclophosphamide|Drug: etoposide|Drug: thiotepa|Procedure: adjuvant therapy|Procedure: autologous bone marrow transplantation|Procedure: bone marrow ablation with stem cell support|Procedure: peripheral blood stem cell transplantation	peripheral blood stem cells	Phase 2	30
30	NCT00003273	Chemotherapy Followed by Peripheral Stem Cell Transplantation in Treating Children With Newly Diagnosed Brain Tumor	Withdrawn	No Results Available	Brain and Central Nervous System Tumors|Neuroblastoma|Rhabdomyosarcoma|Sarcoma	Biological: filgrastim|Drug: carboplatin|Drug: cyclophosphamide|Drug: etoposide|Drug: leucovorin calcium|Drug: methotrexate|Drug: temozolomide|Drug: thiotepa|Drug: vincristine sulfate|Procedure: autologous bone marrow transplantation|Procedure:	peripheral blood stem cells	Phase 2	0
31	NCT00002594	Combination Chemotherapy Followed by Bone Marrow and/or Peripheral Stem Cell Transplantation in Treating Patients With Recurrent Medulloblastoma or CNS Germ Cell Tumors	Completed	No Results Available	Brain Tumor|Central Nervous System Tumor	Biological: Sargramostim|Drug: cyclophosphamide|Drug: melphalan|Procedure: autologous bone marrow transplantation|Procedure: bone marrow ablation with stem cell support|Procedure: peripheral blood stem cell transplantation	peripheral blood stem cells	Phase 2	31

hNSCs: human Neuronal Stem Cells; **SciRT:** Stem cells Radiotherapy; U.S: United States; KR: Korea Republic; CA: Canada; CH: Switzerland; NZ: New Zeland; AU: Australia; AR: Argentina; IE:Ireland; UK: United Kingdom; SCO: Scotland; P.R: Puerto Rico.