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## Mesenchymal stem cells in neurodegenerative diseases: Opinion review on ethical dilemmas

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### Abstract

The treatment of neurodegenerative diseases presents a growing need for innovation in relation to recent evidence in the field of reconstructive therapy using stem cells. Understanding the molecular mechanisms underlying neurodegenerative disorders, and the advent of methods able to induce neuronal stem cell differentiation allowed to develop innovative therapeutic approaches offering the prospect of healthy and perfectly functional cell transplants, able to replace the sick ones. Hence the importance of deepening the state of the art regarding the clinical applications of advanced cell therapy products for the regeneration of nerve tissue. Besides representing a promising area of tissue transplant surgery and a great achievement in the field of neurodegenerative disease, stem cell research presents certain critical issues that need to be carefully examined from the ethical perspective. In fact, a subject so complex and not entirely explored requires a detailed scientific and ethical evaluation aimed at avoiding improper and ineffective use, rather than incorrect indications, technical inadequacies, and incongruous expectations. In fact, the clinical usefulness of stem cells will only be certain if able to provide the patient with safe, long-term and substantially more effective strategies than any other treatment available. The present paper provides an ethical assessment of tissue regeneration through mesenchymal stem cells in neurodegenerative diseases with the aim to rule out the fundamental issues related to research and clinical translation.

**Key words:** Mesenchymal stem cells; Neurodegenerative diseases; Stem cell research; Stem cell therapy; Ethical principles; Patient safety

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**Core tip:** Neurodegenerative diseases constitute a set of pathologies affecting the central nervous system whose main characteristic is a chronic and selective process of neuronal cell death. The study of stem cells and the advent of new methods able to induce neuronal differentiation, is having a significant impact in this sense in recent years, offering the prospect of transplanting healthy and perfectly functional cells, able to replace those diseased. The objective the present paper is to contribute to the construction of an ethical framework that allows a close monitoring of the scientific activity in the experimental and translational fields.

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## INTRODUCTION

Modern transplant surgery presents an impressive need to explore the biological reconstructive possibilities in different branches of medicine. Hence, it is important to deepen the state of the art regarding the clinical applications and ethical implications of cell therapies in neuronal regeneration.

Over the last few years, in the field of tissue grafts in patients suffering from neurodegenerative diseases, a broad perspective has been opened, linked to the possibility of growing in the laboratory differentiated cells and tissues from isolated lines of multipotent cells grown on specific physiological substrates<sup>[1-4]</sup>.

The destruction of the tissue architecture and the impairment of the function of an organ related to the death of the cells of which it is constituted are at the basis of the majority of the pathologies that afflict the population of the industrialized countries<sup>[5]</sup>. Regenerative medicine is a branch of medicine that aims to permanently recover damaged tissues and organs through the exploitation of the regenerative potential of stem cells<sup>[6-8]</sup>. Regenerative medicine, therefore, includes all the therapies that, in pursuing the goal of regeneration, use the potential of stem cells, locally stimulated both to duplicate and to differentiate, to be transferred after appropriate selection and extraction<sup>[9]</sup>.

Understanding the molecular mechanisms underlying neurodegenerative disorders and the advent of methods able to induce neuronal stem cell differentiation have allowed the development of innovative therapeutic approaches offering the prospect of healthy and perfectly functional cell transplants that are able to replace sick ones<sup>[10-13]</sup>.

Mesenchymal stem cells (MSCs) have interesting tissue regenerative potentialities in adult organisms<sup>[14]</sup>. MSCs are available in many tissues and have the capacity to regenerate them in part or entirely once increased in number and differentiated. The use of adult MSCs is currently one of the research areas of greatest interest in regenerative medicine<sup>[15]</sup>.

In recent years, research has focused on the standardization of protocols for the isolation and expansion of MSCs from various tissue sources, on the characterization of their phenotypic and biological properties, and on the development of advanced therapies that combine MSCs with synthetic scaffolds and signalling molecules (growth factors and tissue differentiation) for the construction of hybrid constructs<sup>[16-18]</sup>. In fact, achieving full knowledge of the processes of self-replication and proliferation would allow researchers to obtain an infinite source of tissues for the treatment of degenerative diseases or of important lesions of the central nervous system (CNS).

The optimization of the therapeutic efficacy of MSCs in the treatment of neurodegenerative diseases requires researchers to overcome biological and technical challenges. Particularly, it is necessary to address the critical issues related to the dosage and routes of administration, the identification of patients able to respond to cell replacement therapy, the host's immunological response, the mechanisms of action of the grafts and the adverse effects.

The affirmation of the potential use of MSCs in regenerative medicine, currently

supported by promising scientific results, will allow researchers to meet the high expectations raised in the community only if hinged in a context of transparency and plurality of research, in full respect of different cultural and technical backgrounds<sup>[19,20]</sup>. The protection of plurality makes it possible to deal in depth with the issues of regenerative therapy to understand its mechanisms and to develop effective treatments<sup>[21]</sup>. The lack of the integration of the different perspectives would imply their subtraction from the biological foundations of clinical practice and the exaltation of an empirical medicine incapable of producing new knowledge, depriving the community of the necessary scientificity<sup>[22]</sup>.

Thus, while representing a promising area of tissue transplant surgery and a great achievement in the field of neurodegenerative disease, stem cell research presents certain critical issues that need to be carefully examined from an ethical perspective<sup>[23,24]</sup>.

First, the progress of research must be supported by consolidated and transparent evidence despite the enthusiasm derived from the results of preclinical and clinical trials<sup>[25]</sup>. In fact, the clinical utility of MSCs will be certain only in the presence of safe therapeutic strategies, validated in the long term, that are determined to be substantially more effective than any other available treatment. It is also necessary that the ethical, legal and commercial aspects concerning stem cell research and related clinical trials continue to be discussed on the basis of concrete objectives and through medically objective, scientifically honest and socially useful strategies<sup>[26]</sup>.

In such a context, the use of appropriate methodologies in medical science is crucial for the ability to connect biology and clinical medicine as well as to offer the tools to distinguish good clinical practices from para-scientific illusions<sup>[27]</sup>.

The present paper provides an ethical assessment of tissue regeneration through MSCs in neurodegenerative diseases with the aim outlining the fundamental issues related to research and clinical translation.

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## MSCs IN NEURODEGENERATIVE DISEASES

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The diseases of the CNS represent a heterogeneous category of pathological conditions with distinct etiopathogenetic and symptomatological characteristics, for which a cure has not yet been identified<sup>[28]</sup>. Specifically, neurodegenerative diseases constitute a set of pathologies affecting the CNS whose main characteristic is a chronic and selective process of neuronal cell death. Neuronal deterioration is due to an inevitable loss of brain function that occurs, depending on the type of disease, with cognitive impairment, dementia, motor deficits, and behavioural disorders, more or less serious. Despite the partial overlaps correlated with symptomatology and pathological progression, among the different pathologies studied in tissue regeneration, it is possible to distinguish Parkinson's disease, Alzheimer's disease (AD), Huntington's disease, multiple sclerosis, and amyotrophic lateral sclerosis<sup>[29]</sup>.

The treatment of neurodegenerative diseases presents a growing need for innovation in relation to recent evidence in the field of reconstructive therapy using stem cells<sup>[30,31]</sup>. Hence, it is important to deepen the state of the art regarding the clinical applications of advanced cell therapy products for the regeneration of nerve tissue. At present, there is no cure for neurodegenerative diseases, but there are pharmacological treatments available to counteract some symptoms. The effort of the scientific community is to understand the molecular mechanisms underlying these diseases to intervene with new therapeutic approaches, including genetic approaches. The study of stem cells and the advent of new methods able to induce neuronal differentiation have had a significant impact in this sense in recent years, offering the prospect of transplanting healthy and perfectly functional cells that are able to replace those that are diseased.

MSCs are present in the bone marrow, where they form the stromal counterpart of the haematopoietic stem component, but they are also present in the peripheral blood, in the umbilical cord and in other sites, including muscle tissue, adipose tissue, the synovium, and the periosteum<sup>[32]</sup>. MSCs represent a topic of growing interest and a valid therapeutic alternative in the treatment of neurodegenerative diseases. Currently, MSCs have been studied in the field of several neurodegenerative diseases and acute brain injuries, demonstrating interesting safety profiles in intravenous and intrathecal administration.

Among the different applications under investigation, substantial progress has been recorded in multiple sclerosis, where, consistent with numerous scientific contributions, the administration of human umbilical cord blood-derived MSCs or human bone marrow-derived MSCs has demonstrated an immunomodulatory effect able to provide clinical stabilization, an improvement of the symptoms and a

reduction of the onset of relapse<sup>[33-37]</sup>.

The clinical application of MSCs in the treatment of Parkinson's disease presupposes, on the contrary, the overcoming of numerous challenges in relation to the results obtained in animal models and clinical trials<sup>[38-41]</sup>. The results obtained so far allow cautious optimism in relation to the demonstration of a neurodegenerative effect and a slowing of disease progression in subjects treated with MSCs<sup>[42-44]</sup>.

The therapeutic use of MSCs in AD must still be developed despite extremely high expectations. At present, preclinical evidence supporting the mechanisms of action and potential therapeutic implications is abundant<sup>[45]</sup>. Because of the reliability of the preclinical results, MSC-based therapies have been approved for human trials. Early evidence on the safety and tolerability of the intrathecal administration of allogeneic human umbilical cord blood-derived MSCs, even in the absence of transplant-related adverse events, did not demonstrate significant delays in cognitive decline during follow-up. Despite these results, several other trials are underway to clarify the therapeutic relevance of MSCs and their implications for the course of AD.

Concerning amyotrophic lateral sclerosis, the injection of autologous human bone marrow-derived MSCs into the spinal cord has shown in different studies the ability to induce an improvement of functional assessment scale scores, a better response to treatment and a slowing of disease progression<sup>[46-48]</sup>.

Further clinical studies have demonstrated the potential efficacy of human mesenchymal stem cell administration after ischaemic stroke. Specifically, it has been documented that hBM-MSc transplantation is capable of improving clinical outcomes and reducing mortality rates<sup>[49]</sup>. In addition, an improvement in performance in daily activities and a decrease in cerebral atrophy in patients undergoing autologous hBM-MSc transplantation were noted 6 weeks after the ischaemic event. In some trials aimed at assessing the early effects of treatment, the administration of autologous MSCs after stroke was able to determine a reduction in the size of the infarct area<sup>[50]</sup>.

Again, recent studies have demonstrated that the administration of MSCs promotes recovery in traumatic brain injury due to oxidative stress reduction<sup>[51-54]</sup>. Overall, autologous mesenchymal cell transplantation has highlighted, together with high safety profiles, the ability to support the repair of neurological damage, inducing an improvement in functional performance<sup>[55,56]</sup>.

Finally, as already mentioned, despite the proven potential of MSCs to trigger and regulate the process of neuronal regeneration, several factors limit their clinical translation in neurology. The application difficulties due to the lack of clinical experience, controversies concerning the results obtained and the conflicting conclusions on potential benefits or side effects can be overcome only through a careful discussion of the ethical and regulatory issues related to the subject<sup>[57-59]</sup>.

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## ETHICAL ISSUES RELATED TO STEM CELL RESEARCH AND APPLICATIONS IN NEURODEGENERATIVE DISEASES

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### General principles

For other ethical issues associated with scientific research and clinical medicine, as in the case of stem cell research and applications to transplant therapy, the fundamental criterion of evaluation lies in the defence and promotion of the integral good of the human person, according to its peculiar dignity<sup>[60]</sup>.

In this regard, it is worth remembering that every medical intervention on the human person is subject to limits that are not reduced to the possible technical impossibility of realization but are linked to respect for the same human nature understood in its integral meaning<sup>[61]</sup>.

The most important evaluations regarding the fundamental principles must be directed to the vulnerability of the individual. Neurodegenerative diseases, in fact, determine a state of vulnerability related to the evolution of the disease or to situational factors, which makes patients more susceptible to exploitation. The condition of fragility experienced by the subjects of the experimentation imposes particular care on the part of the investigators in the planning of clinical trials that contemplate fully informed and voluntary participation<sup>[62-64]</sup>. The finding of conditions such as impaired cognitive performance, mental and motor disability, and economic and social disadvantages must lead to the introduction of further guarantees to protect patients' rights and wellbeing as well as safeguards to limit exposure to undue influences<sup>[65]</sup>.

Furthermore, it is necessary to highlight how the defence of research participants' rights presuppose, together with the protection against avoidable damages, a careful evaluation of the benefits for the person and society. Professionals involved in research and clinical trials should prevent physical, psychological, economic and legal

bias with a view to maximize patient advantages.

### **Risk assessment and safety in clinical research**

Historically, some inconsistencies found in the preclinical phase have precluded the clinical translation of some stem-cell-based therapies<sup>[66,67]</sup>. In this context, the therapeutic application of MSCs in animal models provided safety tests that favoured the approval of human clinical trials. Likewise, human experimentation was supported by the ease of the isolation and manipulation of MSCs and by evidence of efficacy related to regenerative and immunomodulatory potentials<sup>[68]</sup>.

Nevertheless, several scientific contributions on the subject of cell therapies emphasize the need to address - in advance of clinical research - the issues of long-term safety, tolerability, and efficacy of the treatments under investigation<sup>[69]</sup>. The cellular product used for research purposes must meet the quality standards required by local legislation through the support of preclinical data that prove the safety of cells, the procedure, and the effective ability of MSCs to differentiate into nerve cells both in the laboratory and in the receiving host. Likewise, the use of mesenchymal stem-cell-based products must be corroborated by precise data on the dose of toxicity, reproductive toxicity, and carcinogenesis.

To date, the main problems are unwanted differentiation, the potential suppression of the anti-tumour response and the neo-angiogenetic capacity of the transplanted MSCs<sup>[70]</sup>. In fact, MSCs have shown paracrine activity with the release of growth factors and cytokines able to stimulate angiogenesis, slow down the processes of cell death and block inflammatory processes. For these reasons, safety studies must be extended to the classification and resolution of possible local complications as well as to systemic adverse effects through the provision of long follow-up periods<sup>[71]</sup>. In fact, clinical practice is the best test for evaluating the adverse effects and limitations of cell therapy regarding the functionality of grafting after transplantation. Based on these assumptions, the safety issues still under debate must be carefully discussed regardless of the promising results obtained from therapies with MSCs.

### **Clinical trials**

MSCs have been or are currently being studied in approximately 46 phase I and II clinical trials ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)). However, not all trials fully meet regulatory criteria, preclinical studies are often weak and insufficient, cellular products are difficult to reproduce in a standardized manner, and results are sometimes supported by poor evidence.

In this regard, it should be noted that, as with any type of pioneering research, no one can provide guarantees of success before the availability of evidence. Hence, it is a duty to pursue every area of research on the sole condition that these are rational, verifiable and methodologically appropriate studies<sup>[72]</sup>.

Therefore, the clinical testing of MSCs requires the definition of unified regulations regarding the procedures for the preparation and maintenance of cellular products with standardized methods and techniques shared between laboratories. Equally evident is the difficulty in obtaining standard reference procedures precisely because of the heterogeneity of both the patients and the original tissue samples, as well as of the expanded cultures.

As outlined in the previous section, the clinical results highlight the overall potential efficacy of MSCs in the treatment of neurodegenerative diseases. Nevertheless, it is desirable that the therapeutic profile of MSCs in the neurological field be further investigated in larger cohorts. This perspective involves meticulous scientific planning aimed at overcoming the obstacles derived from the need to respect the heterogeneity of patients and to refine the inclusion and exclusion criteria.

Moreover, the efficacy of the tested treatments must be proven through different clinical evaluation systems, objective and subjective, included in long follow-up periods in which the integration of diagnostic imaging, laboratory monitoring, functional evaluation and quality of life questionnaires are contemplated.

Finally, the obligation for experimenters in clinical trials to ethically evaluate the commitment of economic and human resources related to the organization of facilities, the clinical management of patients and the traceability of procedures should be noted. Similarly, the analysis of sustainability must include the increased use of resources related to the recruitment of a large cohort, the high turnover of coordinators and dedicated professionals, the possible extension of the study period and follow-up, and the need for the disclosure of results. Obviously, all evaluations on the sustainability and use of resources presuppose, in addition to the intervention of the professionals involved, a huge effort on the part of governments and supranational organizations that finance research and have enormous possibilities for coordination in the allocation of funds and in management of the objectives of the international scientific community.



### **Justice in research and treatment**

The considerations related to justice and equity are issues of remarkable importance, although they are often neglected in the context of scientific research and clinical practice. In the field of new biotechnologies and, in particular, stem-cell-based treatments, the economic costs of products and interventions can be extremely high, as can the time and resources necessary for development and therapeutic use<sup>[73]</sup>. Therefore, it is crucial to focus on the costs and availability of treatments to increase sustainability and reduce inequity in access to care<sup>[74,75]</sup>.

Issues related to justice in the context of MSC research and therapy can be schematically linked to production, biobanking and clinical translation.

Regarding the processing of stem cells and the manufacture of cellular products, there is widespread evidence of a greater effort to standardize and rationalize production in the field of regenerative medicine compared to other branches<sup>[76]</sup>. The development of platform technologies and large-scale production represent an important perspective that can reduce time, labour and costs with interesting ethical implications for access to treatment. However, this strategy is currently poorly practicable in the field of MSCs and “autologous” cell interventions that are certainly more expensive and less readily feasible due to production times. Therefore, in light of the foregoing and with a view to planning future strategies, a careful balance between the needs for cost reduction and accessibility and the implications in terms of safety and effectiveness is essential.

Similar considerations can be formulated regarding the policy and practice of biobanking. Although still at a preliminary stage in technological and regulatory development, stem cell collection, storage and use systems are an indisputable resource for regenerative medicine<sup>[77]</sup>. Ideally, the development of large-scale biobanking systems could lead to an amplification of stem cell assets and a reduction in costs of absolute utility in the implementation of tissue engineering programmes<sup>[78-80]</sup>. The structuring of sustainable systems includes the guarantee of accessibility, the regulation of use in the experimental and therapeutic fields, the refinement of consent in its different forms and the protection of information processes<sup>[81]</sup>. Therefore, large-scale biobanking requires a critical characterization based on a careful assessment of potential benefits as well as practical and ethical challenges.

Finally, it must be stated that all the efforts made in the experimental and clinical field must be supported by scientific transparency and data sharing. In fact, despite the pressures deriving from commercial competition, it is fundamental to protect patients’ hopes and to avoid the feeding of false expectations or, worse, fraudulent therapies<sup>[82-84]</sup>. For these reasons, in consideration of the social and not merely scientific scope of the objectives pursued, it is necessary that the professionals involved consider the ethical implications related to justice as closely related to research and clinical practice.

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## **POSITION STATEMENT**

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Stem cell research and treatment require considerations about different issues of medical, scientific, moral and ethical relevance. The field of MSCs facilitates discussion among stakeholders because it is free from the problems inherent to the use of human embryonic stem cells. However, several issues need an open and constructive debate able to support the rapid development of knowledge and the promising application of MSCs in regenerative medicine.

To prevent the onset of prejudices that can nullify the efforts of the scientific community in such a sensitive area of medical science development, it is necessary to formulate recommendations for good experimental and clinical practice<sup>[85]</sup>.

First, it is desirable to carry out continuous and responsible research aimed at generating evidence on the therapeutic mechanisms of MSCs with regard to differentiation capacity and paracrine activity. The expansion of knowledge must also clarify the persistent doubts about the long-term behaviour and adverse effects of MSCs.

Second, with regard to the future objectives of the research, further studies are suggested on the epigenetics of MSCs, immunogenicity, host immune response, and the stability of the grafts.

Progress in research and therapy requires the codification of universal criteria and standards for the processing of MSCs. For example, the availability of a shared methodology for *in vitro* differentiation could eliminate the limitations resulting from the current poor understanding of the MSC profile.

Moreover, precisely for safety concerns related to the clinical use of MSCs, the

efforts of the scientific community must be aimed at the manufacture of traceable, tolerable and effective cellular products. The translation into clinical practice and the marketing of cellular products presupposes the validation of standardized operating procedures as well as a careful review of the aspects related to functionality, safety and banking.

Ultimately, a significant political and legislative commitment at the international level is needed regarding the approval of public funding able to implement research activities and support clinical translation. The fair distribution of funding and the availability of equal opportunities for researchers determine a liberalization able to accelerate the development of the regenerative approach through MSCs. Only the guarantee of equity in all phases of scientific research will make it possible to respect the principles of justice to protect patients<sup>[85]</sup>.

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## CONCLUSION

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In the heterogeneous and complicated scenario currently characterizing the treatment of neurodegenerative diseases – in terms of the functional needs of patients and research, innovation, resources, and medico-legal issues – a rigorous ethical framework and a strict surveillance of scientific activity in the experimental and translational fields are imperative. It is also necessary that ethical, legal and commercial aspects concerning stem cell research and related clinical trials continue to be discussed on concrete objectives and through strategies that always present themselves as medically objective, scientifically honest and socially useful.

Cell therapies and regenerative medicine, increasingly based on the progress of stem cell biology, have begun to lay the foundations of future clinical practice.

The progress of medical therapy based on MSCs generates multiple expectations but requires a rigorous methodological approach. In particular, a subject so complex and not entirely explored requires a detailed scientific and ethical evaluation aimed at the avoidance of improper and ineffective use rather than incorrect indications, technical inadequacies, and incongruous expectations.

Despite the enthusiasm of stem cell studies, nothing could be more wrong than the transplantation of stem cells in humans without consistent results and consolidated evidence. In fact, the clinical usefulness of stem cell transplantation strategies will be certain only if they are able to provide the patient with safe, long-term and substantially more effective treatments than any other strategy available.

Conclusively, the many challenges still open in the exaltation of the potential of MSCs in the neurological field require an integrated multidisciplinary approach aimed at the contextualization of scientific advances and responsible clinical translation of therapeutic findings. Therefore, the growing focus on the therapeutic implications of MSCs should prompt scientists, physicians, regulatory bodies and bioethicists to act in a coordinated manner to promote appropriate and evidence-based clinical applications.

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## REFERENCES

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- 1 **Volarevic V**, Ljubic B, Stojkovic P, Lukic A, Arsenijevic N, Stojkovic M. Human stem cell research and regenerative medicine—present and future. *Br Med Bull* 2011; **99**: 155-168 [PMID: 21669982 DOI: 10.1093/bmb/ldr027]
- 2 **Wenker SD**, Casali M, Cancedo VC, Casabona JC, Pitossi FJ. Cell reprogramming and neuronal differentiation applied to neurodegenerative diseases: Focus on Parkinson's disease. *FEBS Lett* 2015; **589**: 3396-3406 [PMID: 26226418 DOI: 10.1016/j.v.2015.07.023]
- 3 **Brändl B**, Schneider SA, Loring JF, Hardy J, Gribbon P, Müller FJ. Stem cell reprogramming: basic implications and future perspective for movement disorders. *Mov Disord* 2015; **30**: 301-312 [PMID: 25546831 DOI: 10.1002/mds.26113]
- 4 **Kwak KA**, Lee SP, Yang JY, Park YS. Current Perspectives regarding Stem Cell-Based Therapy for Alzheimer's Disease. *Stem Cells Int* 2018; **2018**: 6392986 [PMID: 29686714 DOI: 10.1155/2018/6392986]
- 5 **Tsukamoto A**, Abbot SE, Kadyk LC, DeWitt ND, Schaffer DV, Wertheim JA, Whittlesey KJ, Werner MJ. Challenging Regeneration to Transform Medicine. *Stem Cells Transl Med* 2016; **5**: 1-7 [PMID: 26607174 DOI: 10.5966/sctm.2015-0180]
- 6 **Kaul H**, Ventikos Y. On the genealogy of tissue engineering and regenerative medicine. *Tissue Eng Part B Rev* 2015; **21**: 203-217 [PMID: 25343302 DOI: 10.1089/ten.TEB.2014.0285]
- 7 **Lanza R**. Regenerative medicine: the last 10 years. *Regen Med* 2016; **11**: 745-746 [PMID: 27911242 DOI: 10.2217/rme-2016-0500]
- 8 **Borro M**, Gentile G, Cipolloni L, Foldes-Papp Z, Frati P, Santurro A, Lionetto L, Simmaco M. Personalised Healthcare: The DiMA Clinical Model. *Curr Pharm Biotechnol* 2017; **18**: 242-252 [PMID: 28183244 DOI: 10.2174/1389201018666170208125131]
- 9 **Mao AS**, Mooney DJ. Regenerative medicine: Current therapies and future directions. *Proc Natl Acad Sci USA* 2015; **112**: 14452-14459 [PMID: 26598661 DOI: 10.1073/pnas.1508520112]
- 10 **Molteni M**, Rossetti C. Neurodegenerative diseases: The immunological perspective. *J Neuroimmunol*

- 2017; **313**: 109-115 [PMID: 29153601 DOI: 10.1016/j.jneuroim.2017.11.002]
- 11 **Pihlström L**, Wiethoff S, Houlden H. Genetics of neurodegenerative diseases: an overview. *Handb Clin Neurol* 2017; **145**: 309-323 [PMID: 28987179 DOI: 10.1016/B978-0-12-802395-2.00022-5]
- 12 **Zhang S**, Tang MB, Luo HY, Shi CH, Xu YM. Necroptosis in neurodegenerative diseases: a potential therapeutic target. *Cell Death Dis* 2017; **8**: e2905 [PMID: 28661482 DOI: 10.1038/cddis.2017.286]
- 13 **Ratcliffe E**, Glen KE, Naing MW, Williams DJ. Current status and perspectives on stem cell-based therapies undergoing clinical trials for regenerative medicine: case studies. *Br Med Bull* 2013; **108**: 73-94 [PMID: 24200742 DOI: 10.1093/bmb/ldt034]
- 14 **Trohatou O**, Roubelakis MG. Mesenchymal Stem/Stromal Cells in Regenerative Medicine: Past, Present, and Future. *Cell Reprogram* 2017; **19**: 217-224 [PMID: 28520465 DOI: 10.1089/cell.2016.0062]
- 15 **Squillaro T**, Peluso G, Galderisi U. Clinical Trials With Mesenchymal Stem Cells: An Update. *Cell Transplant* 2016; **25**: 829-848 [PMID: 26423725 DOI: 10.3727/096368915X689622]
- 16 **Wagey R**, Short B. Isolation, enumeration, and expansion of human mesenchymal stem cells in culture. *Methods Mol Biol* 2013; **946**: 315-334 [PMID: 23179841 DOI: 10.1007/978-1-62703-128-8\_20]
- 17 **Mushahary D**, Spittler A, Kasper C, Weber V, Charwat V. Isolation, cultivation, and characterization of human mesenchymal stem cells. *Cytometry A* 2018; **93**: 19-31 [PMID: 29072818 DOI: 10.1002/cyto.a.23242]
- 18 **Zhou L**, Tu J, Fang G, Deng L, Gao X, Guo K, Kong J, Lv J, Guan W, Yang C. Combining PLGA Scaffold and MSCs for Brain Tissue Engineering: A Potential Tool for Treatment of Brain Injury. *Stem Cells Int* 2018; **2018**: 5024175 [PMID: 30154864 DOI: 10.1155/2018/5024175]
- 19 **Bharadwaj A**. Enculturating Cells: The Anthropology, Substance, and Science of Stem Cells. *Annu Rev Anthropol* 2012; **1**: 303-317 [DOI: 10.1146/annurev-anthro-092611-145710]
- 20 **Sleeboom-Faulkner M**. Stem cell research in Asia: looking beyond regulatory exteriors. *New Gen Soc* 2011; **30**: 137-139 [DOI: 10.1080/14636778.2011.574370]
- 21 **Hardiker NR**, Grant MJ. Factors that influence public engagement with eHealth: A literature review. *Int J Med Inform* 2011; **80**: 1-12 [PMID: 21112244 DOI: 10.1016/j.ijmedinf.2010.10.017]
- 22 **Brown N**, Beynon-Jones SM. 'Reflex regulation': an anatomy of promissory science governance. *Health Risk Soc* 2012; **14**: 223-240 [DOI: 10.1080/13698575.2012.662633]
- 23 **King NM**, Perrin J. Ethical issues in stem cell research and therapy. *Stem Cell Res Ther* 2014; **5**: 85 [PMID: 25157428 DOI: 10.1186/scrt474]
- 24 **Cossu G**, Birchall M, Brown T, De Coppi P, Culme-Seymour E, Gibbon S, Hitchcock J, Mason C, Montgomery J, Morris S, Muntoni F, Napier D, Owji N, Prasad A, Round J, Saprai P, Stilgoe J, Thrasher A, Wilson J. Lancet Commission: Stem cells and regenerative medicine. *Lancet* 2018; **391**: 883-910 [PMID: 28987452 DOI: 10.1016/S0140-6736(17)31366-1]
- 25 **Di Sanzo M**, Cipolloni L, Borro M, La Russa R, Santurro A, Scopetti M, Simmaco M, Frati P. Clinical Applications of Personalized Medicine: A New Paradigm and Challenge. *Curr Pharm Biotechnol* 2017; **18**: 194-203 [PMID: 28240172 DOI: 10.2174/1389201018666170224105600]
- 26 **Frati P**, Scopetti M, Santurro A, Gatto V, Fineschi V. Stem Cell Research and Clinical Translation: A Roadmap about Good Clinical Practice and Patient Care. *Stem Cells Int* 2017; **2017**: 5080259 [PMID: 29090010 DOI: 10.1155/2017/5080259]
- 27 **Mauron A**, Jaconi ME. Stem cell science: current ethical and policy issues. *Clin Pharmacol Ther* 2007; **82**: 330-333 [PMID: 17637783 DOI: 10.1038/sj.cpt.6100295]
- 28 **Wood LB**, Winslow AR, Strasser SD. Systems biology of neurodegenerative diseases. *Integr Biol (Camb)* 2015; **7**: 758-775 [PMID: 26065845 DOI: 10.1039/c5ib00031a]
- 29 **Volkman R**, Offen D. Concise Review: Mesenchymal Stem Cells in Neurodegenerative Diseases. *Stem Cells* 2017; **35**: 1867-1880 [PMID: 28589621 DOI: 10.1002/stem.2651]
- 30 **Lo Furno D**, Mannino G, Giuffrida R. Functional role of mesenchymal stem cells in the treatment of chronic neurodegenerative diseases. *J Cell Physiol* 2018; **233**: 3982-3999 [PMID: 28926091 DOI: 10.1002/jcp.26192]
- 31 **Chang KA**, Lee JH, Suh YH. Therapeutic potential of human adipose-derived stem cells in neurological disorders. *J Pharmacol Sci* 2014; **126**: 293-301 [PMID: 25409785 DOI: 10.1254/jphs.14R10CP]
- 32 **Prockop DJ**, Prockop SE, Bertoncello I. Are clinical trials with mesenchymal stem/progenitor cells too far ahead of the science? Lessons from experimental hematology. *Stem Cells* 2014; **32**: 3055-3061 [PMID: 25100155 DOI: 10.1002/stem.1806]
- 33 **Li JF**, Zhang DJ, Geng T, Chen L, Huang H, Yin HL, Zhang YZ, Lou JY, Cao B, Wang YL. The potential of human umbilical cord-derived mesenchymal stem cells as a novel cellular therapy for multiple sclerosis. *Cell Transplant* 2014; **23** Suppl 1: S113-S122 [PMID: 25385295 DOI: 10.3727/096368914X685005]
- 34 **Mohajeri M**, Farazmand A, Mohyeddin Bonab M, Nikbin B, Minagar A. FOXP3 gene expression in multiple sclerosis patients pre- and post mesenchymal stem cell therapy. *Iran J Allergy Asthma Immunol* 2011; **10**: 155-161 [PMID: 21891821 DOI: 10.03/ijaa.155161]
- 35 **Connick P**, Kolappan M, Crawley C, Webber DJ, Patani R, Michell AW, Du MQ, Luan SL, Altmann DR, Thompson AJ, Compston A, Scott MA, Miller DH, Chandran S. Autologous mesenchymal stem cells for the treatment of secondary progressive multiple sclerosis: an open-label phase 2a proof-of-concept study. *Lancet Neurol* 2012; **11**: 150-156 [PMID: 22236384 DOI: 10.1016/S1474-4422(11)70305-2]
- 36 **Dulamea A**. Mesenchymal stem cells in multiple sclerosis - translation to clinical trials. *J Med Life* 2015; **8**: 24-27 [PMID: 25914733]
- 37 **Cohen JA**, Imrey PB, Planchon SM, Bermel RA, Fisher E, Fox RJ, Bar-Or A, Sharp SL, Skaramagas TT, Jagodnik P, Karafa M, Morrison S, Reese Koc J, Gerson SL, Lazarus HM. Pilot trial of intravenous autologous culture-expanded mesenchymal stem cell transplantation in multiple sclerosis. *Mult Scler* 2018; **24**: 501-511 [PMID: 28381130 DOI: 10.1177/1352458517703802]
- 38 **Gugliandolo A**, Bramanti P, Mazzon E. Mesenchymal stem cell therapy in Parkinson's disease animal models. *Curr Res Transl Med* 2017; **65**: 51-60 [PMID: 28466824 DOI: 10.1016/j.retram.2016.10.007]
- 39 **Venkatesh K**, Sen D. Mesenchymal Stem Cells as a Source of Dopaminergic Neurons: A Potential Cell Based Therapy for Parkinson's Disease. *Curr Stem Cell Res Ther* 2017; **12**: 326-347 [PMID: 27842480 DOI: 10.2174/1574888X12666161114122059]
- 40 **Riecke J**, Johns KM, Cai C, Vahidy FS, Parsha K, Furr-Stimming E, Schiess M, Savitz SI. A Meta-Analysis of Mesenchymal Stem Cells in Animal Models of Parkinson's Disease. *Stem Cells Dev* 2015; **24**: 2082-2090 [PMID: 26134374 DOI: 10.1089/scd.2015.0127]
- 41 **Schwerk A**, Altschüler J, Roch M, Gossen M, Winter C, Berg J, Kurtz A, Akyüz L, Steiner B. Adipose-derived human mesenchymal stem cells induce long-term neurogenic and anti-inflammatory effects and improve cognitive but not motor performance in a rat model of Parkinson's disease. *Regen Med* 2015; **10**:

- 431-446 [PMID: 26022763 DOI: 10.2217/rme.15.17]
- 42 **Mendes Filho D**, Ribeiro PDC, Oliveira LF, de Paula DRM, Capuano V, de Assunção TSF, da Silva VJD. Therapy With Mesenchymal Stem Cells in Parkinson Disease: History and Perspectives. *Neurologist* 2018; **23**: 141-147 [PMID: 29953040 DOI: 10.1097/NRL.0000000000000188]
- 43 **Bagheri-Mohammadi S**, Karimian M, Alani B, Verdi J, Tehrani RM, Nouredini M. Stem cell-based therapy for Parkinson's disease with a focus on human endometrium-derived mesenchymal stem cells. *J Cell Physiol* 2019; **234**: 1326-1335 [PMID: 30146713 DOI: 10.1002/jcp.27182]
- 44 **Park HJ**, Shin JY, Kim HN, Oh SH, Lee PH. Neuroprotective effects of mesenchymal stem cells through autophagy modulation in a parkinsonian model. *Neurobiol Aging* 2014; **35**: 1920-1928 [PMID: 24629674 DOI: 10.1016/j.neurobiolaging.2014.01.028]
- 45 **Shin JY**, Park HJ, Kim HN, Oh SH, Bae JS, Ha HJ, Lee PH. Mesenchymal stem cells enhance autophagy and increase  $\beta$ -amyloid clearance in Alzheimer disease models. *Autophagy* 2014; **10**: 32-44 [PMID: 24149893 DOI: 10.4161/auto.26508]
- 46 **Oh KW**, Moon C, Kim HY, Oh SI, Park J, Lee JH, Chang IY, Kim KS, Kim SH. Phase I trial of repeated intrathecal autologous bone marrow-derived mesenchymal stromal cells in amyotrophic lateral sclerosis. *Stem Cells Transl Med* 2015; **4**: 590-597 [PMID: 25934946 DOI: 10.5966/sctm.2014-0212]
- 47 **Karussis D**, Karageorgiou C, Vaknin-Dembinsky A, Gowda-Kurkalli B, Gomori JM, Kassir I, Bulte JW, Petrou P, Ben-Hur T, Abramsky O, Slavin S. Safety and immunological effects of mesenchymal stem cell transplantation in patients with multiple sclerosis and amyotrophic lateral sclerosis. *Arch Neurol* 2010; **67**: 1187-1194 [PMID: 20937945 DOI: 10.1001/archneurol.2010.248]
- 48 **Mazzini L**, Mareschi K, Ferrero I, Vassallo E, Oliveri G, Boccaletti R, Testa L, Livigni S, Fagioli F. Autologous mesenchymal stem cells: clinical applications in amyotrophic lateral sclerosis. *Neurol Res* 2006; **28**: 523-526 [PMID: 16808883 DOI: 10.1179/016164106X116791]
- 49 **Lee JS**, Hong JM, Moon GJ, Lee PH, Ahn YH, Bang OY; STARTING collaborators. A long-term follow-up study of intravenous autologous mesenchymal stem cell transplantation in patients with ischemic stroke. *Stem Cells* 2010; **28**: 1099-1106 [PMID: 20506226 DOI: 10.1002/stem.430]
- 50 **Honmou O**, Houkin K, Matsunaga T, Niitsu Y, Ishiai S, Onodera R, Waxman SG, Kocsis JD. Intravenous administration of auto serum-expanded autologous mesenchymal stem cells in stroke. *Brain* 2011; **134**: 1790-1807 [PMID: 21493695 DOI: 10.1093/brain/awr063]
- 51 **Hasan A**, Deeb G, Rahal R, Atwi K, Mondello S, Marei HE, Gali A, Sleiman E. Mesenchymal Stem Cells in the Treatment of Traumatic Brain Injury. *Front Neurol* 2017; **8**: 28 [PMID: 28265255 DOI: 10.3389/fneur.2017.00028]
- 52 **Li G**, Yang Y, Dong HJ, Lin L. The research progress of mesenchymal stem cells in the treatment of Traumatic brain injury. *Turk Neurosurg* 2017 [PMID: 28944949 DOI: 10.5137/1019-5149.JTN.20829-17.1]
- 53 **Galindo LT**, Filippo TR, Semedo P, Ariza CB, Moreira CM, Camara NO, Porcionatto MA. Mesenchymal stem cell therapy modulates the inflammatory response in experimental traumatic brain injury. *Neurol Res Int* 2011; **2011**: 564089 [PMID: 21766025 DOI: 10.1155/2011/564089]
- 54 **Fрати A**, Cerretani D, Fiaschi AI, Frati P, Gatto V, La Russa R, Pesce A, Pinchi E, Santurro A, Frascetti F, Fineschi V. Diffuse Axonal Injury and Oxidative Stress: A Comprehensive Review. *Int J Mol Sci* 2017; **18** [PMID: 29207487 DOI: 10.3390/ijms18122600]
- 55 **Anbari F**, Khalili MA, Bahrami AR, Khoradmehr A, Sadeghian F, Fesahat F, Nabi A. Intravenous transplantation of bone marrow mesenchymal stem cells promotes neural regeneration after traumatic brain injury. *Neural Regen Res* 2014; **9**: 919-923 [PMID: 25206912 DOI: 10.4103/1673-5374.133133]
- 56 **Darkazalli A**, Vied C, Badger CD, Levenson CW. Human Mesenchymal Stem Cell Treatment Normalizes Cortical Gene Expression after Traumatic Brain Injury. *J Neurotrauma* 2017; **34**: 204-212 [PMID: 27161121 DOI: 10.1089/neu.2015.4322]
- 57 **Sharma R**. Stem Cells and Tissue Engineering in Medical Practice: Ethical and Regulatory Policies. *Curr Drug Targets* 2019; **20**: 388-398 [PMID: 30173644 DOI: 10.2174/1389450119666180831095830]
- 58 **Fрати P**, Gulino M, Pacchiarotti A, D'Errico S, Sicuro L, Fineschi V. A survey of Italian physicians' opinion about stem cells research: what doctors prefer and what the law requires. *Biomed Res Int* 2014; **2014**: 480304 [PMID: 24877099 DOI: 10.1155/2014/480304]
- 59 **Nagpal A**, Juttner C, Hamilton-Bruce MA, Rolan P, Koblar SA. Stem cell therapy clinical research: A regulatory conundrum for academia. *Adv Drug Deliv Rev* 2017; **122**: 105-114 [PMID: 27760370 DOI: 10.1016/j.addr.2016.10.001]
- 60 **Artal R**, Rubinfeld S. Ethical issues in research. *Best Pract Res Clin Obstet Gynaecol* 2017; **43**: 107-114 [PMID: 28190696 DOI: 10.1016/j.bpobgyn.2016.12.006]
- 61 **Coughlin SS**, Beauchamp TL. Ethics, scientific validity, and the design of epidemiologic studies. *Epidemiology* 1992; **3**: 343-347 [PMID: 1637897 DOI: 10.1097/00001648-199207000-00009]
- 62 **Edwards SJ**, Wilson J. Hard paternalism, fairness and clinical research: why not? *Bioethics* 2012; **26**: 68-75 [PMID: 20459430 DOI: 10.1111/j.1467-8519.2010.01816.x]
- 63 **Coulter A**, Parsons S, Askham J. Where are the patients in decision-making about their own care? Proceeding of the WHO European Ministerial Conference on Health Systems; 2008 Jun 25-27; Tallinn, Estonia. World Health Organization. 2008; 1-26
- 64 **Hammer MJ**. Informed Consent in the Changing Landscape of Research. *Oncol Nurs Forum* 2016; **43**: 558-560 [PMID: 27541548 DOI: 10.1188/16.ONF.558-560]
- 65 **Dhai A**. Exploitation of the vulnerable in research: Responses to lessons learnt in history. *S Afr Med J* 2017; **107**: 472-474 [PMID: 28604315 DOI: 10.7196/SAMJ.2017.v107i6.12437]
- 66 **Daley GQ**, Hyun I, Apperley JF, Barker RA, Benvenisty N, Bredenoord AL, Breuer CK, Caulfield T, Cedars MI, Frey-Vasconcelis J, Heslop HE, Jin Y, Lee RT, McCabe C, Munsie M, Murry CE, Piantadosi S, Rao M, Rooke HM, Sipp D, Studer L, Sugarman J, Takahashi M, Zimmerman M, Kimmelman J. Setting Global Standards for Stem Cell Research and Clinical Translation: The 2016 ISSCR Guidelines. *Stem Cell Reports* 2016; **6**: 787-797 [PMID: 27185282 DOI: 10.1016/j.stemcr.2016.05.001]
- 67 **Pandya SK**. Guidelines for stem cell science and clinical translation. *Indian J Med Ethics* 2016; **1**: 160-161 [PMID: 27348316 DOI: 10.20529/IJME.2016.044]
- 68 **Caprnda M**, Kubatka P, Gazdikova K, Gasparova I, Valentova V, Stollarova N, La Rocca G, Kobylak N, Dragasek J, Mozos I, Prosecky R, Siniscalco D, Büsselberg D, Rodrigo L, Kruzliak P. Immunomodulatory effects of stem cells: Therapeutic option for neurodegenerative disorders. *Biomed Pharmacother* 2017; **91**: 60-69 [PMID: 28448871 DOI: 10.1016/j.biopha.2017.04.034]
- 69 **Trounson A**, McDonald C. Stem Cell Therapies in Clinical Trials: Progress and Challenges. *Cell Stem Cell* 2015; **17**: 11-22 [PMID: 26140604 DOI: 10.1016/j.stem.2015.06.007]

- 70 **Volarevic V**, Markovic BS, Gazzic M, Volarevic A, Jovicic N, Arsenijevic N, Armstrong L, Djonov V, Lako M, Stojkovic M. Ethical and Safety Issues of Stem Cell-Based Therapy. *Int J Med Sci* 2018; **15**: 36-45 [PMID: 29333086 DOI: 10.7150/ijms.21666]
- 71 **Hermansson H**, Hansson OS. A Three-Party Model Tool for Ethical Risk Analysis. *Risk Manag* 2007; **3**: 129-144 [DOI: 10.1057/palgrave.rm.8250028]
- 72 **Bianco P**, Sipp D. Regulation: Sell help not hope. *Nature* 2014; **510**: 336-337 [PMID: 24955467 DOI: 10.1038/510336a]
- 73 **Claxton K**, Briggs A, Buxton MJ, Culyer AJ, McCabe C, Walker S, Sculpher MJ. Value based pricing for NHS drugs: an opportunity not to be missed? *BMJ* 2008; **336**: 251-254 [PMID: 18244997 DOI: 10.1136/bmj.39434.500185.25]
- 74 **Simoens S**. Pricing and reimbursement of orphan drugs: the need for more transparency. *Orphanet J Rare Dis* 2011; **6**: 42 [PMID: 21682893 DOI: 10.1186/1750-1172-6-42]
- 75 **Bubela T**, McCabe C. Value-engineered translation for regenerative medicine: meeting the needs of health systems. *Stem Cells Dev* 2013; **22** Suppl 1: 89-93 [PMID: 24304083 DOI: 10.1089/scd.2013.0398]
- 76 **Hunsberger J**, Harrysson O, Shirwaiker R, Starly B, Wysk R, Cohen P, Allickson J, Yoo J, Atala A. Manufacturing road map for tissue engineering and regenerative medicine technologies. *Stem Cells Transl Med* 2015; **4**: 130-135 [PMID: 25575525 DOI: 10.5966/sctm.2014-0254]
- 77 **Harris DT**. Banking of Adipose- and Cord Tissue-Derived Stem Cells: Technical and Regulatory Issues. *Adv Exp Med Biol* 2016; **951**: 147-154 [PMID: 27837561 DOI: 10.1007/978-3-319-45457-3\_12]
- 78 **Harris DT**. Biobanking and Regenerative Medicine: An Overview. *J Clin Med* 2018; **7** [PMID: 29857481 DOI: 10.3390/jcm7060131]
- 79 **Yong KW**, Choi JR, Wan Safwani WK. Biobanking of Human Mesenchymal Stem Cells: Future Strategy to Facilitate Clinical Applications. *Adv Exp Med Biol* 2016; **951**: 99-110 [PMID: 27837557 DOI: 10.1007/978-3-319-45457-3\_8]
- 80 **Pavón A**, Belouqui I, Salcedo JM, Martin AG. Cryobanking Mesenchymal Stem Cells. *Methods Mol Biol* 2017; **1590**: 191-196 [PMID: 28353271 DOI: 10.1007/978-1-4939-6921-0\_14]
- 81 **Chalmers D**, Rathjen P, Rathjen J, Nicol D. Ethics and Governance of Stem Cell Banks. *Methods Mol Biol* 2017; **1590**: 99-112 [PMID: 28353264 DOI: 10.1007/978-1-4939-6921-0\_7]
- 82 **Oerlemans AJ**, van Hoek ME, van Leeuwen E, Dekkers WJ. Hype and expectations in tissue engineering. *Regen Med* 2014; **9**: 113-122 [PMID: 24351011 DOI: 10.2217/rme.13.89]
- 83 **Turner L**, Knoepfler P. Selling Stem Cells in the USA: Assessing the Direct-to-Consumer Industry. *Cell Stem Cell* 2016; **19**: 154-157 [PMID: 27374789 DOI: 10.1016/j.stem.2016.06.007]
- 84 **Srivastava A**, Mason C, Wagena E, Cuende N, Weiss DJ, Horwitz EM, Dominici M. Part 1: Defining unproven cellular therapies. *Cytotherapy* 2016; **18**: 117-119 [PMID: 26719202 DOI: 10.1016/j.jcyt.2015.11.004]
- 85 **Fрати P**, Frati G, Gulino M, Montanari Vergallo G, Di Luca A, Fineschi V. Stem cell therapy: from evidence-based medicine to emotion-based medicine? The long Italian way for a scientific regulation. *Stem Cell Res Ther* 2013; **4**: 122 [PMID: 24456690 DOI: 10.1186/scri333]



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