Review Article

Access this article online

Quick Response Code:

Website: http://www.braincirculation.org

DOI: 10.4103/2394-8108.192525

Science, ethics and communication remain essential for the success of cell-based therapies

Massimo Dominici, Karen M Nichols[1], Aaron D Levine[2], John EJ Rasko[3,4,5], Miguel Forte[6], Lynn O'Donnell[7], Mickey BC Koh[8,9], Catherine M Bollard[10], Daniel J Weiss[11]

Laboratory of Cellular Therapy, University of Modena and Reggio Emilia, Modena, Italy, [1]NantKwest, Inc., Woburn, MA, [2]School of Public Policy, Georgia Institute of Technology, Atlanta, GA, [7]Department of Internal Medicine, Division of Hematology, The Ohio State University, Columbus, OH, [10]Center for Cancer and Immunology Research, Sheikh Zayed Institute, Children's National Health System, Washington, DC, [11]Department of Medicine, University of Vermont College of Medicine, Burlington, Vermont, USA, [3]Gene and Stem Cell Therapy Program, Centenary Institute, University of Sydney, [5]Department of Cell and Molecular Therapies, Royal Prince Alfred Hospital, Camperdown 2050, [4]Sydney Medical School, University of Sydney, NSW 2006, Australia, [6]TxCell, Valbonne, France, [8]Department of Haematology, St. George's Hospital, London, UK, [9]Cell Therapy Program, Health Sciences Authority, Singapore

Abstract:

Cell-based therapeutics, such as marrow or peripheral blood stem cell transplantation, are a standard of care for certain malignancies. More recently, a wider variety of cell-based therapeutics including the use of mesenchymal stromal/stem cells, T-cells, and others show great promise in a wider range of diseases. With increased efforts to expand cell-based treatments to several clinical settings, many institutions around the world have developed programs to explore cellular therapy's potential for safe and effective applications. In legitimate investigations, usually conducted through academic centers or biotechnology industry-sponsored efforts, these studies are regulated and peer-reviewed to ensure safety and clear determination of potential efficacy. However, in some cases, the use of cell-based approaches is conducted with insufficient preclinical data, scientific rationale, and/or study plan for the diseases claimed to be treated, with patients being charged for these services without clear evidence of clinical benefit. In this context, patients may not be properly informed regarding the exact treatment they are receiving within a consenting process that may not be completely valid or ethical. Here, the authors emphasize the importance of distinguishing "proven cell-based therapies" from "unproven" and unauthorized cell-based therapies. This publication also addresses the necessity for improved communication between the different stakeholders in the field, patient associations, and advocacy groups in particular, to favor medical innovation and provide legitimate benefits to patients. Considering the progressive growth of cell-based treatments, their increasing therapeutic value and the expectation that society has about these therapies, it is critically important to protect patients and ensure that the risk/benefit ratio is favorable. This paper is a review article. Literature referred to in this paper has been listed in the references section. The datasets supporting the conclusions of this article are available online by searching PubMed. Some original points in this article come from the laboratory practice in our research centers and the authors' experiences.

Key words:

Communication, informed consent, medical tourism, mesenchymal stem/stromal cells, regulations, stem cells, unproven cell therapies

Introduction

New cell-based treatments are currently emerging throughout the world, and significant effort is being made to safely translate these products to clinical settings. As the process of translating these medical innovations to the bedside progresses, a surprising number of clinics have begun marketing treatments directly to patients with dubious scientific rationale, safety, and/or efficacy data. As a result, many patients undergo treatments without a clear understanding of risks and benefits and without a full educated and informed consent. A growing body of literature on this topic demonstrates the wide and diversified nature of the issue and its global impact on public health.[1-5]

Unproven Cell-based Therapies

In general, the safety and efficacy of any potential therapeutic product should be established

Address for correspondence:
Dr. Massimo Dominici, Laboratory of Cellular Therapy, University of Modena and Reggio Emilia, Via Del Pozzo, 71, Modena, Italy.
E-mail: massimo.dominici@unimore.it

Submission: 16-09-2016
Revised: 28-09-2016
Accepted: 28-09-2016

How to cite this article: Dominici M, Nichols KM, Levine AD, Rasko JE, Forte M, O'Donnell L, *et al*. Science, ethics and communication remain essential for the success of cell-based therapies. Brain Circ 2016;2:146-51.

through legitimate regulated peer-reviewed clinical trials. While there are successes, many new drugs and other potential therapies fail to meet endpoints of safety or efficacy studies. Some are clear failures while others are found to be ineffective or minimally effective compared to available treatments and therefore abandoned for financial or other reasons.[6,7] For rare incurable diseases for which there are no treatment options, regulatory agencies are progressively establishing accelerated processes with the ability to assess and eventually approve in a timely manner the compassionate use of therapies still under clinical study.[8,9] A case in point is the recent approval of a medication by the US FDA for Duchenne muscular dystrophy based on arguably inadequate and limited clinical trial data, thus expanding access to potentially beneficial therapeutic products.[10] These aggressive risk/benefit approaches, where less is known about the new proposed therapeutic based on limited data but the patient has no other options, can potentially be justified. However, unfortunate precedents may be set from decisions of this sort resulting in desperate patients and family members pushing even harder for unproven therapies through legitimate agencies.[11,12] Further, these types of deliberations are still within the boundaries of legitimate clinical trials conducted under appropriate regulatory oversight and do not address the larger issue of the wider and increasing use of unproven therapies, also referred to as stem cell medical tourism, both in the US and around the world.

While defining unproven cell therapy may be a difficult exercise, a recent International Society for Cellular Therapy (ISCT) publication aimed at this purpose.[13] The authors indicate that the following features may apply to unproven approaches: (a) an unclear scientific rationale to suggest potential efficacy, (b) the lack of understanding of the mechanism of action and/or the biological function to support clinical use, (c) insufficient data from *in vitro* assays, animal models, and clinical studies regarding the safety profile to support the use in patients, (d) the lack of a standardized approach to confirm product quality and ensure consistency in cell manufacturing, (e) an inadequate information disclosed to patients to enable proper informed consent, (f) the use within nonstandardized or nonvalidated administration methods, and (g) the introduction of uncontrolled experimental procedures in humans.

New Potential Cell-based Therapies and Regulatory Considerations

Recent advances in basic and preclinical research on immune cells, stem cells, and progenitor cells have led to a worldwide effort to bring cell-based therapies to clinical applications.[14,15] The fact that most of these cell types are relatively easy to isolate presents a remarkable opportunity to increase translational studies to treat still lethal or debilitating diseases. Stem cells, including induced pluripotent stem cells, retain the potential to save impaired organs and restore damaged tissue.[16,17] Other progenitor cells, such as mesenchymal stromal/stem cells (MSCs), can also serve as immune regulatory cells when not directly contributing to the repair of damaged structural tissue.[18] For example, the ability of MSC to affect immune cell function has led to their testing as immunomodulatory agents for the treatment of graft versus host disease, a devastating and often lethal complication of allogeneic bone marrow transplantation.[19]

Further, advances in technology as well as in intellectual property considerations have enabled an increase in commercially available cell manufacturing and storage devices and in reagents that facilitate the selection, storage, processing, and expansion of cells more efficiently and at lower costs than available previously. While all of these advances allow acceleration toward a clinical setting, the general availability of these technologies has also resulted in an increase of putative cellular therapies that have not been sufficiently investigated to ensure both safety and efficacy and to balance the risks and the benefits during treatment. This is particularly misleading because many of these treatments are inaccurately marketed as if they were proven despite insufficient scientific rationale and/or clinical trial efficacy data.

Most of the cell types being clinically studied or prematurely marketed come from tissues in the body that can be easily accessed such as bone marrow, blood, and fat. Furthermore, there are relatively few barriers with respect to technology and intellectual property rights in comparison to those limiting the advancement of chemically synthesized molecules or biologics that are associated with more complex production methods and property rights. Regulatory guidelines for the use of cell-based technologies have not always kept up, even in more advanced countries, such as in the USA.[20] While various evolving systems of risk-based approaches to impose lower regulatory constraints may facilitate an increase of legitimate treatments, an unintended consequence has been the quasi-legitimization of unproven treatments with dubious efficacy, safety, and/or questionable scientific rationales.[21,22] In countries with less developed manufacturing and clinical practice regulations,[2,23,24] these unproven treatment clinics may operate essentially unchecked. Nevertheless, even more developed regulatory frameworks currently seem incapable of limiting all unproven approaches.[2,11,20]

This is a critical issue and calls for novel and complementary strategies wherein the scientific, medical, and pharmaceutical communities and patient associations to collaborate to face this global challenge. However, economic and political conditions in many countries complicate any harmonization process because the diverse environments that exist worldwide resulting in numerous social, ethical, regulatory, economic, and logistical barriers.[25] Furthermore, the approach to health care varies by country. Along with an awareness of the difficulty and complexity in trying to make a decision about medical treatment for a patient in dire circumstances, it is also necessary to acknowledge the diverse impetuses held by individual stakeholders.

Patients and Their Expectations

None of us can put ourselves in the position of desperately ill patients and their families seeking any possible cure or treatment. Unfortunately, this is what many outfits offering unproven therapies take advantage of, and frequently the primary reason why patients seek out unproven cell therapies is because they view such cell therapies (e.g., stem cell therapies) as "magic."[9] This is an expectation and also fostered in part by popular media and by incomplete understanding of what stem cells are and/or current understanding of what cell-based therapies can or cannot do. This information is often

beyond the scope of what the general population is aware of knowledgeable about and it is up to caregivers, scientific groups, and patient advocacy groups to be a resource of more accurate information. The unproven cell-based approaches come in a variety of guises and are frequently presented to patients as proven or accepted therapies without adequately addressing efficacy.[20] Thus, there is deliberate deception often phrased in ways that seem convincing or that are otherwise misleading. One example of this is presenting the unproven therapy under the guise of a clinical trial, even being listed on the US clinicaltrials.gov website. However, as has been recently addressed by the NIH and US Congress, the clinicaltrials.gov website may be misleading as to the veracity of what is actually listed. A concerted effort is currently underway to revamp this website to include only legitimate trials that have appropriate oversight and follow through.[26]

Further, there are also often understated or poorly disclosed risks associated with the various procedures and approaches as clinics offering unproven approaches may not fully disclose or may minimize possible procedure or treatment risks. Safety profiles may be offered, but these are frequently based on inadequate follow-up, patient testimonials, and the absence of legitimate standardized Phase I clinical trial safety data. These types of positive assertions and claims regarding any particular unproven cell therapy are compounded considering that after treatment patients may return home away from any given clinic with no reliable or significant follow-up and insufficient information to provide their local healthcare practitioners. To emphasize this concern, reports of short- and long-term complications related to unproven cell-based therapies are increasing including hemorrhage, malignant transformation, and death.[27-29]

While all of these considerations should guide rationale development and validation of potential new cell-based therapies, they are often of less import to desperate patients seeking cures. As such, an additional consideration is that even in the event of adverse reactions, patients and their families might not disclose such toxicities due to fears of embarrassment, legal, and social ramifications including media exposure. Thus, both clinics and patients themselves may hide severe adverse effects that could emerge after administration of an unproven cell therapy.

Financial considerations also are significant issue. The underlying motivation of many clinics is to be profitable and thus exorbitant, unregulated, and generally poorly justifiable fees are often charged for unproven cell-based therapies. This adds financial hardship and stress to many patients. This makes it all the more essential that caregivers, scientific groups, patient advocacy groups, and above all regulatory agencies effectively communicate with patients and address unrealistic expectations from such therapies.

Marketing of Unproven Cell Therapies and How Health-care Providers Can Help

How patients access information regarding these unproven cell therapies is also a focus of concern as these treatments are often marketed via unauthorized open social channels (i.e., websites, social media, magazine advertisements, etc.) that are not supervised or regulated by any medical or regulatory agencies, which can monitor claims made through other marketing channels. While currently the definition of legitimate cell treatments lies in the hands of national regulatory agencies for medicinal and therapeutic products, harmonizing regulations and establishing universally shared definitions would also facilitate the development of proper communication strategies. However, economic and political conditions in many countries complicate any harmonization process because such diverse environments exist worldwide resulting in numerous social, ethical, regulatory, economic, and logistical barriers.[25]

The primary reason why patients seek out unproven cell therapies is because they view such therapies as magical treatments to their disease that is not being cured or improved by available treatments.[30] Unproven approaches are, however, generally so expensive that some patients have to seek loans to cover the costs of such procedures, placing a great financial burden on themselves and their relatives.[31] This makes it essential that treating clinicians take in charge of their responsibility to effectively communicate with patients and address unrealistic expectations from such therapies. Without an accurate and realistic understanding of the safety and function true potential for the benefit of the cell treatment being offered, patients cannot possibly give appropriate informed consent or accurately evaluate the value of being treated.

Furthermore, the approach to health care varies by country. Along with an awareness of the difficulty and complexity of trying to make a decision about medical treatment for a patient in dire circumstances, it is also necessary to acknowledge the diverse motivations held by individual stakeholders. These range from the economically incentivized capitalist to the optimistic or/unrealistic scientists, who intentionally or unintentionally, muddle the scientific evidence by their diverse motivations. Regrettably, this leads to the exploitation of vulnerable patient populations. For the sake of improved health and better patient care, it is essential that all involved stakeholders speak with a unified voice to regulate cell therapy and clearly delineate for patients the safety and efficacy profile of each cell therapeutic based on strong scientific rationale and rigorous clinical trials.

Determining a Clear Path to Establish Proven Cellular Therapies

Living cells differ from pharmaceutical products, necessitating a different approach to study their pivotal features. They have the potential not only to circulate throughout the body but also to integrate into diverse tissues and organs. In addition, cells may change in response to the tissue microenvironment, prompting challenges in standardization. Furthermore, cells release diverse compounds, such as cytokines, which can be produced based on underlying pathophysiological condition. Cell heterogeneity makes it difficult to test cellular products with the same standards as stable drugs. Despite these challenges, it is possible to establish some potency measures and evaluate the safety/efficacy of cell-based products.[15,32] Thus, scientists and clinicians must present rigorous and verifiable evidence to those who wish to provide cell-based treatments. Translational studies focused on cell-based therapies face challenges similar to those faced in the early development of

monoclonal antibodies,[33] yet monoclonal antibodies are now commonly used to successfully treat multiple diseases in a very large number of patients. Therefore, scientists and clinicians, albeit without the pressure that now exists in cellular therapy, were able to overcome these barriers by providing evidence of rigorous assessments. Hence, it is critical to determine the evidence indicating that a specific cell therapy is effective and safe and can be considered a viable approach for the treatment of a specific disease.

The scientific process and principles involving cell therapies are already reasonably defined. First, clear proof based on *in vitro* investigations and, when applicable, on legitimate preclinical animal models providing evidence with distinctive cells must be provided. Subsequently, well-designed and regulated clinical trials with reproducible approaches and data must be presented. There should also be a follow-up conducted to ensure evidence of short- and long-term safety. In addition, during clinical trial development, studies aimed to further clarify the possible mechanism(s) of action of any given cell therapy for any given human disease should be encouraged.[34]

One common method of treatment is to administer autologous therapies in which cells are isolated from the patient's own tissues and then infused back into the same patient. An example would be the use of autologous, adipose-derived MSC. While this therapeutic approach is commonly considered safer than other cell-based interventions due to lack of immunogenicity, it must still be evaluated by defined end points to determine efficacy depending on the target indication. A scientific rationale should exist that addresses the aim of the autologous therapeutic intervention and the evidence behind it, including any data regarding anticipated adverse events and the mechanism of action of how the cells treat the target indication. The primary question is: What data are in the investigator's possession or retrievable in the peer-reviewed literature supporting that the approach might be safe and efficacious? Moreover, in many clinical situations, investigations must be conducted long-term to determine the clinical effects.

It has also been established that in the case of difficult medical situations in which all treatment options have been exhausted, cell-based therapies undergoing clinical investigation can be administered on a compassionate use basis. Although regulations about compassionate use-based care vary, each situation must be handled with the same degree of rigor and include, at a minimum, assessment of the alternatives available to the patient, preliminary evidence of the safety of the proposed intervention, and appropriate reporting on the treatment and any adverse event. Compassionate use care does not typically gather evidence that contributes the establishment of a cellular therapy as proven, and care should be taken by both regulators and clinical trial sponsors to ensure that compassionate use care does not compromise ongoing clinical research aiming to establish a therapy as safe and effective. This will simultaneously allow for innovation as well as patient care as a key aspect of medicine within defined boundaries.[35]

The quantity and quality of data is a significant aspect of defining a therapy as proven and effective for a condition. Similar to other novel potential therapies, it would first require a well-designed and regulated investigation evaluating the plausibility and safety of specific doses, timing, and routes of administration of the treatment. This initial study would be followed by further investigations, based on the maximum tolerated/utilized safe dose determined in the first study, on the efficacy of the therapy when administered to larger populations of patients.

In addition, disagreements may arise regarding the way that cells are obtained and handled *ex vivo*, an example being the situation of the minimally manipulated autologous cells.[36] The debate still exists as to whether or not these cells should be regarded as possible therapeutic products for nonhomologous uses[37,38] or simply as the practice of medicine when they are not manipulated in specific ways. Regardless of the situation, it is essential that all treatments undergo rigorous review to establish their safety and efficacy and be regulated before being named an official treatment. It is important to construct a framework for rational advancement in which peer-reviewed science and clinical development will exist in a mutual relationship focused on benefitting the patient.

Awareness and Communication to Promote Safe and Effective Treatments

Several scientific organizations across the world, including the ISCT, are committed to increasing public awareness concerning the outlined complexity of unproven cellular therapies and the need for concerted action.[13,39,40] These organizations support increased opportunities for discussion and the creation of documents that improve the information available to stakeholders in the field.[30] They are also interested in dissecting crucial features of the so-called unproven cellular therapies[41] in an attempt to increase communication between patient associations, health-care providers, and the patients themselves, emphasizing the necessity for proper research before administering treatments. One of the ISCT's main objectives is to encourage cooperation and to establish updatable, multi-lingual, web-available documents that generate opportunities to continue building a strong foundation for empirically based safe treatments.

Proper communication and access to the current standard of care across the world is necessary to promote the legitimate development of new treatments. The ethical and social dilemmas that arise will be difficult to remove from the decision-making process, and adjustments will have to be made. Nonetheless, it is essential to implement independent review mechanisms to make sure that performing treatment is motivated by concern for the patient rather than the interests of an outside body or financial gain for the physician. Moving forward, data from various innovations must be reviewed to promote further advancement in the field.[42] In accordance with the type of cell therapy and the diseases, review and regulation should be carried out at the national as well as international level. In summary, cell-based interventional therapies embody the potential to treat a wide variety of diseases. However, they must be studied and evaluated in the most rigorous manner possible to ensure the safety and most economical and effective care for the patient.

Acknowledgment

This work is supported by the Presidential Task Force on unproven cellular therapies of the International Society for

Cellular Therapy (ISCT). We are grateful to Rony Ganon (former Regional Affairs and Education Coordinator, ISCT, Vancouver, Canada), to Queenie Jang (Executive Director, ISCT, Vancouver, Canada) and to Ms. Shaila Ghanekar (University of South Florida, Tampa, US) for their valuable support in this project.

Financial support and sponsorship

The manuscript and related research have been supported by the project of the International Society for Cellular Therapy (ISCT).

Conflicts of interest

There are no conflicts of interest.

References

1. O'Donnell L, Turner L, Levine AD. Part 6: The role of communication in better understanding unproven cellular therapies. Cytotherapy 2016;18:143-8.
2. Berger I, Ahmad A, Bansal A, Kapoor T, Sipp D, Rasko JE. Global distribution of businesses marketing stem cell-based interventions. Cell Stem Cell 2016;19:158-62.
3. Sipp D, Pei D. Bioethics in China: No wild East. Nature 2016;534:465-7.
4. Levine AD, Wolf LE. The roles and responsibilities of physicians in patients' decisions about unproven stem cell therapies. J Law Med Ethics 2012;40:122-34.
5. Munsie M, Hyun I. A question of ethics: Selling autologous stem cell therapies flaunts professional standards. Stem Cell Res 2014;13(3 Pt B):647-53.
6. Hefti FF. Requirements for a lead compound to become a clinical candidate. BMC Neurosci 2008;9 Suppl 3:S7.
7. Kwong E, Higgins J, Templeton AC. Strategies for bringing drug delivery tools into discovery. Int J Pharm 2011;412:1-7.
8. Available from: http://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/default.htm. [Last accessed on 2016 Sep 16].
9. Available from: http://www.fda.gov/Drugs/ResourcesForYou/HealthProfessionals/ucm313768.htm. [Last accessed on 2016 Sep 16].
10. Available from: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm521263.htm. [Last accessed on 2016 Sep 16].
11. Carrozzi M, Amaddeo A, Biondi A, Zanus C, Monti F, Alessandro V. Stem cells in severe infantile spinal muscular atrophy (SMA1). Neuromuscul Disord 2012;22:1032-4.
12. Margottini L. Stem cells. Italian Parliament orders €3 million trial of disputed therapy. Science 2013;340:1028.
13. Dominici M, Nichols K, Srivastava A, Weiss DJ, Eldridge P, Cuende N, *et al.* Positioning a scientific community on unproven cellular therapies: The 2015 International Society for Cellular Therapy perspective. Cytotherapy 2015;17:1663-6.
14. Rao M, Mason C, Solomon S. Cell therapy worldwide: An incipient revolution. Regen Med 2015;10:181-91.
15. Srijaya TC, Ramasamy TS, Kasim NH. Advancing stem cell therapy from bench to bedside: Lessons from drug therapies. J Transl Med 2014;12:243.
16. Sharma RR, Pollock K, Hubel A, McKenna D. Mesenchymal stem or stromal cells: A review of clinical applications and manufacturing practices. Transfusion 2014;54:1418-37.
17. Drews K, Jozefczuk J, Prigione A, Adjaye J. Human induced pluripotent stem cells – from mechanisms to clinical applications. J Mol Med (Berl) 2012;90:735-45.
18. Horwitz EM, Dominici M. How do mesenchymal stromal cells exert their therapeutic benefit? Cytotherapy 2008;10:771-4.
19. Le Blanc K, Davies LC. Mesenchymal stromal cells and the innate immune response. Immunol Lett 2015;168:140-6.
20. Turner L, Knoepfler P. Selling stem cells in the USA: Assessing the direct-to-consumer industry. Cell Stem Cell 2016;19:154-7.
21. Blight A, Curt A, Ditunno JF, Dobkin B, Ellaway P, Fawcett J, *et al.* Position statement on the sale of unproven cellular therapies for spinal cord injury: The international campaign for cures of spinal cord injury paralysis. Spinal Cord 2009;47:713-4.
22. Scadden D, Srivastava A. Advancing stem cell biology toward stem cell therapeutics. Cell Stem Cell 2012;10:149-50.
23. Regenberg AC, Hutchinson LA, Schanker B, Mathews DJ. Medicine on the fringe: Stem cell-based interventions in advance of evidence. Stem Cells 2009;27:2312-9.
24. Gunter KC, Caplan AL, Mason C, Salzman R, Janssen WE, Nichols K, *et al.* Cell therapy medical tourism: Time for action. Cytotherapy 2010;12:965-8.
25. Nichols K, Janssen W, Wall D, Cuende N, Griffin D. Part 4: Interaction between unproven cellular therapies and global medicinal product approval regulatory frameworks. Cytotherapy 2016;18:127-37.
26. Hudson KL, Lauer MS, Collins FS. Toward a new era of trust and transparency in clinical trials. JAMA. 2016. doi: 10.1001/jama.2016.14668. [Epub ahead of print].
27. Amariglio N, Hirshberg A, Scheithauer BW, Cohen Y, Loewenthal R, Trakhtenbrot L, *et al.* Donor-derived brain tumor following neural stem cell transplantation in an ataxia telangiectasia patient. PLoS Med 2009;6:e1000029.
28. Berkowitz AL, Miller MB, Mir SA, Cagney D, Chavakula V, Guleria I, *et al.* Glioproliferative lesion of the spinal cord as a complication of "stem-cell tourism". N Engl J Med 2016;375:196-8.
29. Albini T. Severe Visual Loss After Intravitreal Injection of Autologous Adipose Tissue Derived Stem Cells for Age-related Macular Degeneration. Oral Presentation at the "FDA Workshop: Scientific Evidence in Development of HCT/ps Subject to Premarket Approval". Washington DC; 8 September, 2016.
30. Deans RJ, Gunter KC, Dominici M, Forte M. Part 5: Unproven cell therapies and the commercialization of cell-based products. Cytotherapy 2016;18:138-42.
31. McLean AK, Stewart C, Kerridge I. Untested, unproven, and unethical: The promotion and provision of autologous stem cell therapies in Australia. Stem Cell Res Ther 2015;6:12.
32. Galipeau J, Krampera M, Barrett J, Dazzi F, Deans RJ, DeBruijn J, *et al.* International Society for Cellular Therapy perspective on immune functional assays for mesenchymal stromal cells as potency release criterion for advanced phase clinical trials. Cytotherapy 2016;18:151-9.
33. Baker DA, Harkonen WS. Regulatory agency concerns in the manufacturing and testing of monoclonal antibodies for therapeutic use. Targeted Diagn Ther 1990;3:75-98.
34. Bravery CA, Carmen J, Fong T, Oprea W, Hoogendoorn KH, Woda J, *et al.* Potency assay development for cellular therapy products: An ISCT review of the requirements and experiences in the industry. Cytotherapy 2013;15:9-19.
35. Lindvall O, Hyun I. Medical innovation versus stem cell tourism. Science 2009;324:1664-5.
36. Official Journal of the European Union. Regulation (EC) No 1394/2007 of the European Parliament and of the Council on Advanced Therapy Medicinal Products and Amending Directive 2001/83/EC and Regulation (EC) No. 726/2004; 2007. Available from: http://www.ec.europa.eu/health/files/eudralex/vol-1/reg_2007_1394/reg_2007_1394_en.pdf. [Last accessed on 2015 Oct 08].
37. Ferry N. European Medicines Agency. CAT's Views on Classification of ATMPs: Homologous Use. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2015/04/WC500185222.pdf. [Last accessed on 2015 Oct 08].

38. Human cells, tissues, and cellular and tissue-based products. Fed Regist 2015;21:1271. To be codified at 7 CFR §1271.3. Available from: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=1271.3. [Last accessed on 2015 Oct 08].
39. Available from: http://www.closerlookatstemcells.org. [Last accessed on 2016 Sep 16].
40. Wagner DE, Cardoso WV, Gilpin SE, Majka S, Ott H, Randell SH, *et al.* An Official American Thoracic Society Workshop Report 2015. Stem cells and cell therapies in lung biology and diseases. Ann Am Thorac Soc 2016;13:S259-78.
41. Srivastava A, Mason C, Wagena E, Cuende N, Weiss DJ, Horwitz EM, *et al.* Part 1: Defining unproven cellular therapies. Cytotherapy 2016;18:117-9.
42. Main H, Munsie M, O'Connor MD. Managing the potential and pitfalls during clinical translation of emerging stem cell therapies. Clin Transl Med 2014;3:10.