Stem Cell Research (2014) 13, 647–653

Available online at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/scr

REVIEW

A question of ethics: Selling autologous stem cell therapies flaunts professional standards

Megan Munsie [a,*], Insoo Hyun [b]

[a] Stem Cells Australia, Department of Anatomy and Neuroscience, The University of Melbourne, Parkville 3010, Australia
[b] Department of Bioethics, School of Medicine, Case Western Reserve University, Cleveland, OH 44106-4976, USA

Received 23 January 2014; received in revised form 15 April 2014; accepted 22 April 2014
Available online 29 April 2014

Abstract The idea that the body's own stem cells could act as a repair kit for many conditions, including cardiac repair, underpins regenerative medicine. While progress is being made, with hundreds of clinical trials underway to evaluate possible autologous cell-based therapies, some patients and physicians are not prepared to wait and are pursuing treatments without evidence that the proposed treatments are effective, or even safe. This article explores the inherent tension between patients, practitioners and the need to regulate the development and commercialization of new cellular therapies — even when the cells come from the patient.

Contents

Introduction

The possibility that stem cells could act as a repair kit to restore function following disease or injury has long been heralded as the next revolution in medicine. Although there remain few established stem cell-based treatments beyond

* Corresponding author at: Level 2, Melbourne Brain Centre, 30 Royal Parade, The University of Melbourne, Parkville, Victoria 3010, Australia.
E-mail address: megan.munsie@unimelb.edu.au (M. Munsie).

http://dx.doi.org/10.1016/j.scr.2014.04.014

the use of hematopoietic stem cell (HSC) transplants for leukemia and certain other diseases of the blood and immune system (Daley, 2012), extensive media coverage has fuelled community expectation as it depicts stem cell research much closer to clinical application than in reality it is. For example, while most clinical trials over the last decade were early phase studies using stem cells for cancer and graft-versus-host disease, the majority of newspaper articles during the same period focused on the potential use of stem cells for neurological conditions, cardiovascular disease and diabetes (Bubela et al, 2012). Heightened community expectation is also reflected in survey data where perceptions of the benefits of stem cell research are far greater than perceptions of risk (DIISR, 2010; Downey and Geransar, 2008).

For many who look to stem cells as a means to alleviate their suffering, or that of their loved one, such high expectations are unlikely to be met in the near future. Although the number of clinical trials for novel applications of stem cells has risen rapidly since 2004 (Li et al, 2013), the majority of the trials are focused on establishing safety with enrollment duly limited. Frustrated by the lack of access to clinical trials, many have turned to those offering stem cell treatment outside clinical trials (Kiatpongsan and Sipp, 2009; Lau et al, 2008; Petersen et al, 2013).

In the information age, finding a 'stem cell' therapy is not difficult. A simple on-line search will reveal numerous websites that rely extensively on compelling patient testimonials to promote their treatment and leave the viewer with the impression that a cure is "but a simple injection away" (Ogbogu et al, 2013; Petersen and Seear, 2011). Some providers offer to use the patient's own stem cells – so called autologous treatments – while others claim to use donated sources of stem cells including fetal tissue, cord blood and human embryos. However, what is exactly being delivered to the patient – and indeed if it even contains stem cells – is often difficult to ascertain as few providers have independent verification of the products they administer. The mode of delivery of the cells also varies, with some providers using intramuscular or intravenous injections, while others use intrathecal or intracranial delivery of the cells (Lau et al, 2008; Petersen et al, 2013). Claiming to be able to treat conditions as diverse as spinal cord injury, heart disease, cerebral palsy, multiple sclerosis, asthma, arthritis and chronic fatigue syndrome, the websites offer little in the way of scientific evidence to justify these "optimistic portrayals of stem cell treatments"(Petersen and Seear, 2011).

Although not as frequently promoted as orthopedic and neurological applications, 'stem cell' treatments to improve cardiac function are offered. For example, an Australian patient sought treatment in Thailand for his heart disease and diabetes using ex vivo expanded bone-marrow cells stating that there was a marked improvement in his heart's ejection fraction—"rising from below 20% to over 50%" following the treatment (Stem Cell China News, 2009). Such treatments are expensive with many relying on community fundraising to enable their treatment (Petersen et al, 2013), as can be seen from the following extract taken from a wife's plea for help for her husband:

> "Our family and friends have done a lot of research… stem cells are harvested from his blood and then put back into his heart…. After speaking to several couples that have gone through exactly the same as us, our belief is that this is the better road…. Although this is what we so desperately want, we have exhausted all of our funds."
>
> [GoFundMe (2012)]

While concern about patients traveling abroad to seek out stem cell treatments not available at home has been well documented, with the term 'stem cell tourism' used to describe this phenomenon (Kiatpongsan and Sipp, 2009; Master and Resnik, 2011; Ryan et al, 2010), it is what is happening in our 'own backyard' in relation to autologous treatments that requires closer examination and is the focus of this paper.

Rise of autologous 'stem cell' therapies

The idea that you can use your own stem cells is highly appealing for many patients. Simple messages – such as the cells won't be rejected; that the risk of a disease is avoided, and that using your own cells is more 'ethical' – resonate in the community and are reinforced in direct-to-consumer marketing strategies employed by providers. Indeed those opposing the use of human embryos in research have long promoted adult stem cell treatments as a more ethically acceptable alternative, despite criticisms that such portrayals fail to acknowledge that the cited treatments await clinical validation (Smith et al, 2006) — a warning that can still be leveled at many promoting autologous cell treatments today.

To a large extent the growth in unproven autologous stem cell treatments has been enabled by the use of liposuction techniques. Despite calls by the American Society of Plastic Surgeons and the American Society of Aesthetic Plastic Surgery warning that 'stem cell' face-lifts and breast augmentation are "not adequately supported by clinical evidence" (Eaves et al, 2012), cosmetic surgeons have started to offer these services to their clientele. In Australia, cosmetic surgeons and others are going well beyond localized administration of cells derived from liposuction for esthetic surgery. For less than $10,000 Australian patients are being offered intra-articular injections of adipose-derived cell extracts for osteoarthritis and cartilage repair, as well as intravenous delivery of crude cellular extract for stroke, multiple sclerosis, retinal neuropathy, spinal cord injury, Amyotrophic Lateral Sclerosis and even autism. All of these treatments are being offered as a medical procedure outside clinical trials.

The underlying justification for such adipose-derived procedures is the assumption that the cellular extract contains mesenchymal stem cells (MSCs) — a type of stromal cell isolated from a wide variety of sources including bone marrow, fat, dental pulp and placental tissue and one of the most common sources of stem cells in new clinical trials over the last decade (Li et al, 2013). For the providers they are an attractive source as they are relatively easy to isolate from the patient, are reputed to be able to form cartilage, bone and muscle, and also exert immunomodulatory properties enabling them to act as an "injury drugstore" (Caplan and Correa, 2011). However, what are exactly MSCs and their use in regenerative medicine – and even whether they should be

called stem cells – is a matter of significant debate within the scientific community (Bianco et al, 2013a; Shen, 2013).

Interestingly, autologous cell therapies are often promoted as being 'natural' and having 'no risk' because they come from 'you'. However, safety should not be assumed in all circumstances. The recent report of bone fragments growing around a patient's eye following a stem cell facelift (Jabr, 2012), as well as the lesions that developed in the kidney of a woman who received marrow-derived cells (Thirabanjasak et al, 2010), highlights the potential hazards of early adoption of unproven stem cell treatments — even when the cells come from the patient.

Curbing provision of unproven stem cell treatments

In recognition of the growth of commercial practices marketing unproven stem cell treatments, the International Society for Stem Cell Research (ISSCR) in 2007 established a task force of scientific, medical, and bioethical experts to develop a comprehensive set of performance guidelines for the clinical translation of stem cell research. These guidelines address any attempt to develop novel clinical applications of stem cells and their direct derivatives, including the use of HSCs and other somatic stem cells outside their established standards of care, specifically voicing concern about the "potential physical, psychological, and financial harm to patients who pursue unproven stem cell-based therapies and the general lack of scientific transparency and professional accountability of those engaged in these activities" (Hyun et al., 2008; ISSCR, 2008).

In particular these guidelines included a series of recommendations for the responsible administration of unproven stem cell interventions outside a clinical trial context. The ISSCR guidelines allow some room for medical innovation during the course of patient care through the provision of unproven stem cell interventions, but only under very special circumstances (Lindvall and Hyun, 2009). These exceptional circumstances involve just small numbers of seriously ill patients who would be cared for under a stringent set of oversight requirements including independent peer review of the proposed innovative stem cell procedure and its scientific rationale, institutional accountability, rigorous informed consent and careful patient monitoring, transparency, speedy adverse-event reporting, and a committed plan by clinician-scientists to move toward a formal clinical trial after experience with the intervention in a few patients (Hyun et al., 2008).

For all other circumstances that do not meet the criteria governing responsible stem cell-based innovative care, the ISSCR included an additional clear statement within the guidelines entitled 'Position on Unproven Commercial Stem Cell Interventions.' This position statement articulates in no uncertain terms that "the ISSCR condemns the administration of unproven uses of stem cells or their direct derivatives to a large series of patients outside of a clinical trial, particularly when patients are charged for such services. Scientists and clinicians should not participate in such activities as a matter of professional ethics." (ISSCR, 2008, p. 5).

In 2013, following a rise in the number of providers of autologous-based stem cell treatments, the ISSCR released an additional statement reiterating the criteria under which stem cell research should be translated – even when the cells are from the patient – and calling on medical licensing bodies, legal authorities, patient advocacy organizations, physicians, and others to exercise their influence to discourage commercial provision of unproven autologous cell-based interventions outside of clinical trials (ISSCR, 2013).

However, regulating this area is proving to be extremely challenging with autologous-based cell therapies often able to be couched as 'medical practice' and therefore able to avoid the exacting standards imposed by regulators regarding manufacturing and evaluation standards (DeFrancesco, 2012; Sipp, 2013). A recent ruling from the US Court of Appeals for the District of Columbia Circuit provides some guidance. In this case the appellants were unable to convince the Court that the administration of ex vivo expanded autologous MSCs – derived from bone marrow or synovial fluid – was a medical procedure and upheld the right of the Food and Drug Administration (FDA) to regulate the manufacture of this product (United States v. Regenerative Sciences and LLC, 2014). However, FDA's rights to regulate all autologous cell therapies – especially where there is less extensive ex vivo manipulation – remain to be tested.

In other jurisdictions such as Australia there are no such caveats with respect to the degree of manipulation. Under regulations introduced in 2011, autologous cell therapies provided by registered Australian doctors do not have to comply with stringent requirements set by local regulators of medicines and devices — the Therapeutic Goods Administration (Trickett and Wall, 2011). Rather such practices are seen as medical practices where oversight falls within the remit of the Australian Health Practitioner Regulatory Agency. Although simple modifications to the Australian regulations – such as incorporating recognition of the inherent risks in extending the use of cells beyond what they usually do in the body (i.e. non-homologous use) and making it a requirement that cells are prepared in accredited laboratories – could enhance the oversight and curb unproven practices, many Australian scientists and clinicians fear that such changes will not occur until there are serious adverse outcomes.

Expected standards in medical practice

Attempts by clinicians to frame autologous stem cell treatments under the aegis of medical practice do not shield these treatments from further ethical scrutiny. While it is true that physicians normally enjoy a considerable degree of freedom in deciding how to best treat their patients, it is also true that there exists a series of medical professional norms that constrain the range of this discretionary therapeutic privilege. It is worth highlighting that the ISSCR's position statement on unproven commercial stem cell therapies makes a direct appeal to the notion of professional ethics, and in this way brings medical professionalism into the discussion.

Even if one assumes for the sake of argument that the FDA and other relevantly similar regulatory agencies do not have jurisdiction over the administration of autologous stem cell therapies, physicians are still constrained by the standards of medical professional ethics. In fact, medical professionalism calls on doctors to abide by a code of conduct that is

inconsistent with the offer to sell patients unproven autologous commercial stem cell therapies.

Perhaps the most well-known recent articulation of such a set of medical professional standards is provided in the Physician Charter, which was drafted by the American Board of Internal Medicine (ABIM) Foundation, the American College of Physicians Foundation, and the European Federation of Internal Medicine (ABIM Foundation, 2002). This document is applicable to physicians worldwide, and it was published simultaneously in *The Annals of Internal Medicine* and *The Lancet* in 2002 (ABIM Foundation, 2002). The Physician Charter reaffirms the aspirational ideal that physicians must place the interests of their patients above their own personal interests, including their own private financial motivations. Market forces must not compromise the principle of the primacy of patient welfare. The Physician Charter then goes on to elucidate the many professional responsibilities of physicians, three of which are especially relevant to the selling of unproven stem cell therapies.

The first professional responsibility involves the medical profession's collective interest in ensuring that all of its members are competent medical practitioners. This commitment to competence calls on physicians to work collaboratively with other professionals to reduce medical error and increase patient safety. Related to this commitment to competence is the physician's professional responsibility to support and foster scientific knowledge. As the Charter states:

> Much of medicine's contract with society is based on the integrity and appropriate use of scientific knowledge and technology. Physicians have a duty to uphold scientific standards, to promote research, and to create new knowledge and ensure its appropriate use. The profession is responsible for the integrity of this knowledge, which is based on scientific evidence and physician experience.
>
> [ABIM Foundation (2002, p. 245)]

Finally, the Charter reminds us that professionalism requires physicians to manage their financial conflicts of interests carefully and rigorously, since failure to do so could undermine the principle of primacy of patient welfare.

Together, these three professional responsibilities – a commitment to medical competence, a commitment to scientific knowledge and evidence, and the need to avoid financial conflicts of interest – militate against the proposition that proffering unproven commercial stem cell therapies to patients is ethically unproblematic for physicians. The norms of medical professionalism make it very difficult to justify the view that physicians should be free to offer whatever they want to patients without answering to anyone else, let alone an outside group like the ISSCR. As members of the medical profession, physicians are minimally ethically required to engage in a process of self-regulation whereby members of that profession are obligated to accept internal evaluation and external scrutiny of all major aspects of their professional performance. Physicians are also obligated by these norms to offer their patients only therapies that are scientifically well-grounded and are open to independent critical review by domain experts.

Such views that place special moral obligations on health professionals are prevalent, long-standing, and justifiable. Physicians are granted the special privilege of tending to the ill only because of an implicit contractual premise that the proper social role of the physician is to use his or her special knowledge for the general welfare of society. A physician is not entitled to exploit his or her special knowledge for personal gain alone, as business entrepreneurs may. The moral duties of non-maleficence (first do no harm) and beneficence (promote the welfare of others) are central to understanding the medical profession as a social institution that lies outside the commercial marketplace. According to commercialism, the primary ethical obligations that matter are that the seller does not coerce, cheat, or defraud others. The principle of *caveat emptor* (buyer beware) governs all other aspects of the seller–buyer relationship. The physician–patient relationship, on the other hand, is a fiduciary bond whereby the doctor has a moral duty to look after the best interests of the patient. This fiduciary relationship, which characterizes all physician–patient interactions, is derived from the power differential that exists between the expert and the non-expert and the non-expert's vulnerability caused by illness and his or her necessary trust in the doctor (Brody, 1992).

Because power differentials and vulnerability are not inherent components of the commercial relationship, it is inappropriate to try to squeeze the physician–patient relationship into the framework of commercial transactions and consumers' marketplace freedom. The physician's professional moral duties of patient beneficence and non-maleficence require him or her to offer only medical treatments that are supported by an evidence-based approach. These two moral duties, combined with the medical professional's other commitment to scientific knowledge and rigor, undermine the position that physicians ought to be able to sell unproven stem cell therapies to any patient who is willing to purchase them. The rules of the marketplace ignore the special moral character of the medical profession.

Community demand and expectation

Unfortunately, autologous stem cell therapies continue to be presented and viewed under a commercialistic social lens which remains insensitive to the medical professional norms just described. This makes it all too easy for clinicians to offer these treatments as a matter of free consumer choice. For those seeking to benefit from stem cell research, the promise of stem cells understandably offers great 'hope' (Petersen et al, 2013), with the ability to access possible therapies using your own cells even more attractive. A recent study of Australians who have pursued stem cell treatments abroad highlights that few look beyond the financial costs (Petersen et al, 2013). Commenting on her decision to take her child abroad for an autologous-based stem cell treatment one participant stated:

> It came down to the worst that could happen was nothing really, the worst that could happen was we could spend our money and… gotten no result.
>
> [Petersen et al (2013)]

Not only are the potential risks to health rarely acknowledged by patients – even when highly invasive

techniques are used to deliver the cells – but also there is a degree of ownership about 'my cells'. For example, in reaction to steps taken by the FDA in relation to the practices of a company in Texas which was expanding MSCs taken from abdominal fat, clients and those looking to use this service were outraged that the government was telling them what they could do with their bodies (Aldhous, 2013) and an online campaign was mounted to press congress to protect American's right to "access our own stem cells" (Patients for Stem Cells, 2013).

Perhaps the most graphic illustration of the tension between patients, providers, scientists and regulators is what has been happening in Italy. In response to moves by the Italian government to restrict access to unproven treatments, aggrieved protesters have blocked traffic and stormed parliament to make their frustration known. For many years the Stamina Foundation had been treating patients, including many children, with unproven cell therapies by reputedly using MSCs extracted and expanded from the patient's own bone marrow or from allogeneic sources (Bianco et al, 2013b). Following an inspection of their facilities in 2012 Agenzia Italiana del Farmaco (AIFA) – the Italian Medicines Agency – intervened to stop the treatments due to concerns about how the cells were prepared. There ensured a very public exchange in the media between those calling for caution and the need for regulation, and those demanding 'compassionate use' of this therapy to be allowed for these sick and dying patients (Abbott, 2013). In response to the public pressure, the Senate passed permissive legislation to remove cell therapies from the oversight of AIFA thereby enabling Stamina to continue to offer treatment. This was subsequently modified to limit treatment to current patients in a government funded clinical trial provided that European Union regulations were met including that cells were manufactured in compliance with Good Manufacturing Practice and that an expert panel was convened to oversee the trial design (Margottini, 2013a). However a resolution on the rights or otherwise of Stamina to provide treatment remains a long way from being reached. A series of recent developments has seen the expert panel state that there was "no scientific foundation" to justify the trial and called for it to be abandoned (Margottini, 2013b), only to be followed by Stamina instigating successful legal action to have the expert committee declared invalid (Abbott, 2014). While a new committee is to be appointed, for those at the center of this turbulent dispute – the patients and their families – their frustration no doubt continues.

However not all patients are satisfied with what they have paid for. Patients in Japan have recently commenced legal action following unsatisfactory outcomes from autologous adipose-derived treatments (Sakagami and Yoneyama, 2013), others in the US have sued for failure to deliver on anti-aging claims (Cyranoski, 2012) and in Italy, there is also an ongoing fraud investigation into Stamina Foundation's activities (Margottini, 2013b). While negative publicity and punitive findings associated with these cases may restrict the activities of individual providers, and dampen enthusiasm of others, this may not be enough to slow the commercialization of autologous stem cell therapy. While in many countries, most notably in the US, the market regulation of goods and services can occur through the personal injury (torts) legal system, this post hoc means of regulation is non-ideal because serious harms must first be suffered by patients and their families. Preventive regulation that reinforces medical professional ethical duties more proactively should be the preferred route to managing autologous stem cell therapies.

Looking forward

There has been considerable effort expended on increasing awareness in the community about the risks of pursing stem cell treatment outside clinical trials (ASCC, 2009; ISSCR, 2010; Master and Caulfield, 2014; NSCFA, 2013). With patients rarely acknowledging risk other than financial risk associated with perusing treatment abroad using donated sources (Petersen et al., 2013), the blatant promotion of 'natural' and 'no risk' autologous stem cell interventions posses a new and concerning development. This is particularly so given that the framing of such treatment is heavily influenced by an inherent conflict of interest. While providers selling such interventions place them as part of legitimate medical practice and others as a possible innovative medicine, the basic premise of assessment of risks against benefits by the independent regulators should remain paramount. Although some patients and providers may see this as interference resulting in an unnecessary delay in potentially 'life-saving' treatment, as stated in a recent commentary highlighting the dangers of doing translational medicine in reverse, "extraordinary claims" should require "extraordinary evidence" (Bianco, 2013).

Patient demand should not be met by providing unproven treatments in a commercial context, especially at the expense of important professional scientific and medical norms. However, it needs to be recognized that this will not be persuasive for many who see stem cells as their only hope. Managing such unmet community expectation is going to take "more than providing decision makers with the right information" (Hyun, 2013). Health and medical professionals need to acknowledge and more proactively manage the hope that patients and their families invest in stem cell science (Hyun, 2013; Petersen et al, 2013). We need to continue to encourage hope in medical research, including stem cell research, but recognize that clinical translation of basic research takes time. We need to address the misconception that it is the regulators that are 'costing you your life', and we need to remind clinicians and the public of the social importance of medical professionalism and the fiduciary nature of the doctor–patient relationship. While steps to curb the sale of autologous-based cell interventions through addressing regulatory ambiguity and reinforcing existing standards of medical professional and ethical conduct are welcomed and essential, this needs to be done in a concert with managing community expectations.

Abbreviations

ABIM	American Board of Internal Medicine
AIFA	Agenzia Italiana del Farmaco
ASCC	Australian Stem Cell Centre
FDA	US Food and Drug Administration
HSCs	hematopoietic stem cells

ISSCR	International Society for Stem Cell Research
MSCs	mesenchymal stem or stromal cells
NSCFA	National Stem Cell Foundation of Australia
US	United States of America

Acknowledgments

MM is a member of Stem Cells Australia, a Special Research Initiative in Stem Cell Science funded by the Australian Research Council.

References

Abbott, A., 2013. Stem-cell ruling riles researchers. Nature 495 (7442), 418–419.

Abbott, A., 2014. Leaked files slam stem-cell therapy. Nature 505 (7482), 139–140. http://dx.doi.org/10.1038/505139a.

ABIM Foundation, 2002. Medical professionalism in the new millennium: a physician charter. Ann. Intern. Med. 136 (3), 243–246.

Aldhous, P., 2013. Fight for the right to stem cells. New Sci. 219 (2929), 42–45.

ASCC: Australian Stem Cell Centre, 2009. Stem Cell Therapies: Now and in the Future. The Australian Stem Cell Centre Patient Handbook. ASCC, Melbourne (December).

Bianco, P., 2013. Don't market stem-cell products ahead of proof. Nature 499 (7458). http://dx.doi.org/10.1038/499255a (255-255).

Bianco, P., Cao, X., Frenette, P.S., Mao, J.J., Robey, P.G., Simmons, P.J., Wang, C.Y., 2013a. The meaning, the sense and the significance: translating the science of mesenchymal stem cells into medicine. Nat. Med. 19 (1), 35–42. http://dx.doi.org/10.1038/nm.3028.

Bianco, P., Barker, R., Brüstle, O., Cattaneo, E., Clevers, H., Daley, G.Q., Smith, A., 2013b. Regulation of stem cell therapies under attack in Europe: for whom the bell tolls. EMBO J. 32 (11), 1489–1495. http://dx.doi.org/10.1038/emboj.2013.114.

Brody, H., 1992. The Healer's Power. Yale University Press.

Bubela, T., Li, M.D., Hafez, M., Bieber, M., Atkins, H., 2012. Is belief larger than fact: expectations, optimism and reality for translational stem cell research. BMC Med. 10 (1), 133. http://dx.doi.org/10.1186/1741-7015-10-133.

Caplan, A.I., Correa, D., 2011. The MSC: an injury drugstore. Cell Stem Cell 9 (1), 11–15. http://dx.doi.org/10.1016/j.stem.2011.06.008.

Cyranoski, D., 2012. Patients seek stem-cell compensation. Nature News Blog (online 6 July). http://blogs.nature.com/news/2012/07/patients-seek-stem-cell-compensation.html (Accessed 17 December 2013).

Daley, G.Q., 2012. The promise and perils of stem cell therapeutics. Cell Stem Cell 10 (6), 740–749. http://dx.doi.org/10.1016/j.stem.2012.05.010.

DeFrancesco, L., 2012. Adult stem cell therapies walk the line. Nat. Biotechnol. 30 (8), 739–741. http://dx.doi.org/10.1038/nbt.2321.

DIISR: Department of Innovation, Industry, Science and Research, 2010. Public attitudes towards biotechnology in Australia. http://www.innovation.gov.au/industry/nanotechnology/PublicAwarenessandEngagement/Documents/AustBioAttitude2010.pdf (Accessed 17 December 2013).

Downey, R., Geransar, R., 2008. Stem cell research, publics' and stakeholder views. Health Law Rev. 16 (2), 69–85.

Eaves III, F.F., Haeck, P.C., Rohrich, R.J., 2012. ASAPS/ASPS position statement on stem cells and fat grafting. Plast. Reconstr. Surg. 129 (1), 285–287. http://dx.doi.org/10.1097/PRS.0b013e3182362caf.

GoFundMe, 2012. Retired NRL player needs adult stem cells (Online 29 July). http://www.gofundme.com/xm5ag (Accessed 17 December 2013).

Hyun, I., 2013. Therapeutic hope, spiritual distress, and the problem of stem cell tourism. Cell Stem Cell 12 (5), 505–507.

Hyun, I., Lindvall, O., Ährlund-Richter, L., Cattaneo, E., Cavazzana-Calvo, M., Cossu, G., et al., 2008. New ISSCR guidelines underscore major principles for responsible translational stem cell research. Cell Stem Cell 3 (6), 607–609. http://dx.doi.org/10.1016/j.stem.2008.11.009.

ISSCR: International Society for Stem Cell Research, 2008. Guidelines for the clinical translation of stem cells. http://www.isscr.org/docs/default-source/clin-trans-guidelines/isscrglclinicaltrans.pdf (Accessed 17 December 2013).

ISSCR, 2010. Take a closer look at stem cell research treatments (7 December). http://www.closerlookatstemcells.org (Accessed 17 December 2013).

ISSCR, 2013. Statement on delivery of unproven autologous cell-based interventions to patients (online 11 September). http://www.isscr.org/docs/default-source/isscr-statements/isscr-acbistatement-091113-fl.pdf (Accessed 17 December 2013).

Jabr, F., 2012. In the flesh: the embedded dangers of untested stem cell cosmetics. Scientific American (17 December). http://www.scientificamerican.com/article.cfm?id=stem-cell-cosmetics (Accessed 10 November 2013).

Kiatpongsan, S., Sipp, D., 2009. Monitoring and regulating offshore stem cell clinics. Science 323 (5921), 1564–1565. http://dx.doi.org/10.1126/science.1168451.

Lau, D., Ogbogu, U., Taylor, B., Stafinski, T., Menon, D., Caulfield, T., 2008. Stem cell clinics online: the direct-to-consumer portrayal of stem cell medicine. Cell Stem Cell 3 (6), 591–594. http://dx.doi.org/10.1016/j.stem.2008.11.001.

Li, M.D., Atkins, H., Bubela, T., 2013. The global landscape of stem cell clinical trials. Regen. Med. 9 (1), 1–13. http://dx.doi.org/10.2217/rme.13.80.

Lindvall, O., Hyun, I., 2009. Medical innovation versus stem cell tourism. Science 324, 1664–1665. http://dx.doi.org/10.1126/science.1171749.

Margottini, L., 2013a. Italian Parliament orders clinical trial of controversial stem cell treatment. Science Insider (online 22 May). http://news.sciencemag.org/europe/2013/05/italian-parliament-orders-clinical-trial-controversial-stem-cell-treatment (Accessed 9 April 2014).

Margottini, L., 2013b. No point in testing controversial stem cell treatment, Italian panel says. Science Insider (online 12 September). http://news.sciencemag.org/biology/2013/09/no-point-testing-controversial-stem-cell-treatment-italian-panel-says (Accessed 17 December 2013).

Master, Z., Caulfield, T., 2014. Patient booklet: what you need to know about stem cell therapies. http://www.stemcellnetwork.ca/index.php?page=patientbooklet&hl=eng (Accessed 9 April 2014).

Master, Z., Resnik, D.B., 2011. Stem-cell tourism and scientific responsibility. EMBO Rep. 12 (10), 992–995. http://dx.doi.org/10.1038/embor.2011.156.

NSCFA: National Stem Cell Foundation of Australia, 2013. The Australian Stem Cell Handbook. July NSCFA, Melbourne (http://www.stemcellfoundation.net.au/patient-information/handbook [Accessed 17 December 2013]).

Ogbogu, U., Rachul, C., Caulfield, T., 2013. Reassessing direct-to-consumer portrayals of unproven stem cell therapies: is it getting better? Regen. Med. 8 (3), 361–369. http://dx.doi.org/10.2217/rme.13.15.

Patients for Stem Cells, 2013. Tell your Senator — protect our right to adult stem cells (online 14 June). http://www.patientsforstemcells.org/tell-your-senator-protect-our-right-to-adult-stem-cells/ (Accessed 17 December).

Petersen, A., Seear, K., 2011. Technologies of hope: techniques of the online advertising of stem cell treatments. New Genet. Soc. 30 (4), 329–346.

Petersen, A., Seear, K., Munsie, M., 2013. Therapeutic journeys: the hopeful travails of stem cell tourists. Sociol. Health Illn. http://dx.doi.org/10.1111/1467-9566.12092 (Epub ahead of print).

Ryan, K.A., Sanders, A.N., Wang, D.D., Levine, A.D., 2010. Tracking the rise of stem cell tourism. Regen. Med. 5 (1), 27–33. http://dx.doi.org/10.2217/rme.09.70.

Sakagami, H., Yoneyama, K., 2013. 'Stem cell treatments' mar trust The Japan News (online 5 December). http://the-japan-news.com/news/article/0000846173 (Accessed 17 December 2013).

Shen, H., 2013. Stricter standards sought to curb stem-cell confusion. Nature 499, 389. http://dx.doi.org/10.1038/499389a.

Sipp, D., 2013. Direct-to-consumer stem cell marketing and regulatory responses. Stem Cells Transl. Med. 2 (9), 638–640. http://dx.doi.org/10.5966/sctm.2013-0040.

Smith, S., Neaves, W., Teitelbaum, S., 2006. Adult stem cell treatments for diseases. Science 313 (5786), 439.

Stem Cell China News, 2009. Heart disease — Kevin (online 16 February). http://stemcellschina.com/es/heart-disease-kevin (Accessed 17 December 2013).

Thirabanjasak, D., Tantiwongse, K., Thorner, P.S., 2010. Angiomyeloproliferative lesions following autologous stem cell therapy. J. Am. Soc. Nephrol. 21 (7), 1218–1222. http://dx.doi.org/10.1681/ASN.2009111156.

Trickett, A.E., Wall, D.M., 2011. Regulation of cellular therapy in Australia. Pathology 43 (6), 627–634.

United States v. Regenerative Sciences and LLC, 2014. http://www.gpo.gov/fdsys/pkg/USCOURTS-dcd-1_10-cv-01327 (12-5254 (D. C. Cir. 2014) (On line 4 February)) (Accessed 9 April).