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REVIEW

The unregulated commercialization of stem cell treatments: a global perspective

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Abstract **Research into the biological properties and clinical potential of stem cells has spurred strong public investment, industry development, media coverage, and patient interest in recent years. To date, however, few clinical applications of demonstrated safety and efficacy have been developed with the exception of uses of hematopoietic stem cells in the treatment of diseases of the blood and immune systems. This lack of an evidence basis notwithstanding, hundreds of companies and private clinics around the world now sell putative stem cell treatments for an enormously broad range of medical and quality-of-life conditions. This represents a major challenge for legitimate scientists working in the field, for authorities seeking to protect their constituencies, and for patients and consumers targeted by such companies' marketing strategies. In this review, I provide an overview of the global industry in pseudomedical stem cell treatments, with an investigation of claims in a single disease area (amyotrophic lateral sclerosis), and make recommendations for the introduction and enforcement of appropriate regulatory responses to this problem.**

Keywords stem cell tourism; medical ethics; stem cell policy and regulation; alternative medicine

Introduction

Stem cells, which are generally defined operationally as cells capable of self-renewal and differentiation into multiple cell types, have demonstrably effective uses in the treatment of numerous disorders affecting the blood and immune systems. In addition to such well-established applications of hematopoietic stem cells harvested from the bone marrow, peripheral blood, or umbilical cord, hundreds of academic and industry-funded clinical studies are under way investigating the safety and/or efficacy of stem cell-based interventions for a broad spectrum of medical conditions including diabetes [1], spinal cord injury [2], stroke [3], and multiple sclerosis [4], among others. Importantly, however, at the time of this writing no randomized, blinded, multicenter clinical trial of sufficient statistical power to yield generalizable data has shown efficacy in any of these conditions exceeding that of the currently available standard of care.

Despite the current lack of a scientific basis for medical applications of stem cells outside of established uses in the reconstitution or modulation of the blood or immune system, a large number of privately owned clinics and companies now market injections of stem cells for the treatment of an extraordinarily diverse group of diseases, ranging from life-threatening conditions such as amyotrophic lateral sclerosis [5–7], Parkinson's disease [8], and HIV/AIDS [9], to genetic disorders such as Down's syndrome [10], to cosmetic enhancements such as breast augmentation [11] and hair regrowth [12]. Indeed, one prominent website owned by the founder of a Thai stem cell treatment company lists more than 180 medical conditions that it claims can be treated by adult stem cells [13]. Similarly, the operator of a clinic based in New Delhi, India has claimed in a patent application that her proprietary method for the clinical use of human embryonic stem cells can be used in a remarkably broad group of diseases that "include, without limitation, cancer, liver and kidney disorders, nervous system disorders, skin disorders, autoimmune disorders, genetic disorders, eye disorders, musculoskeletal disorders, fertility and reproductive disorders and cardiovascular disorders," in addition to dozens of other specifically named diseases [14].

The variety of stem cell types that companies purport to use

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in such unregulated interventions is similarly extensive. Clinics in various locales have advertised human embryonic stem (ES) cells [15], and fetal stem cells [16], as well as applications of autologous and allogeneic mesenchymal or hematopoietic stem cells, derived from bone marrow [5], umbilical cord blood [17], adipose tissue [18], or other sources. In addition to these unfounded claims regarding human stem cells, other businesses have emerged that claim medical uses for animal and plant stem cells, or for nutritional supplements intended to activate or cause the proliferation of endogenous stem cells [19]. It must be noted that in the absence of independent oversight, it is impossible to verify whether such companies deliver pure quantities of the cell types they market, and incidents have been reported in which cells injected into patients were a heterogeneous slurry of human cells [20], or indeed of entirely non-human origin [21].

The low operating costs and low regulatory burdens afforded by situating treatment centers in developing economies and online marketing techniques, coupled with the enormous profit potential enabled by recruiting patients from wealthy countries, has resulted in the rapid growth of an industry based on the un- or under-regulated clinical use of stem cells of various sorts. More than 300 such companies advertising primarily in the English language have been identified (unpublished data). Additionally, it has been estimated that Russia also has hundreds of stem cell clinics [22], while a noted Chinese bioethicist stated that between 100 and 150 such companies were operating in that country as of 2009 [23].

The geographical scope of the problem is broad in terms of the location of treatments centers, and patient recruitment and pre-treatment operations, as well as the points of origin for their patient clientele. Active treatment centers can be found in highly regulated nations including the United States [24], Japan [25], and Germany [5], in emerging biomedical powers, such as China [26] and India [27], as well as in many countries that are not generally recognized as originators of frontline medical innovation, such as Ecuador [28], Panama [29], the Dominican Republic [30], the Philippines [18], the Seychelles [31], Kazakhstan [32], and the United Arab Emirates [33]. Statistics on the countries of origin of patients are not generally available, but a review of aggregations of patient blogs and testimonials, such as the website China Stem Cell News, suggest that patients travel from a diverse range of locations in North America, Europe, the Middle East and Asia [34].

The rapidity and scale of the growth of this unregulated commercialization of pseudomedical uses of stem cells has prompted extensive commentary and criticism by bioethicists, media organizations, and academic societies. Studies have focused on the lack of scientific basis for claims made on stem cell clinic websites [35], analyses of media accounts [36] and patient blogs [37], summaries of regulatory challenges [38], and overviews of the general scope of the industry [39,40] and its expansion into alternative medicine [19]. Numerous reports have been published in English-language media (one recent study identified more than 300 such accounts), and coverage appears to have become more positive in recent years [36]. Organizations representing the international stem cell research community have additionally issued statements of concern [41–43] as well as information resources for prospective patients [44].

Regulatory responses have varied in different jurisdictions. Some countries, such as Costa Rica [45], the Netherlands [46], and Hungary [47], have been able to prevent the opening of or shut down stem cell clinics within their borders. Other countries, including Thailand [48] and China [49], have enacted regulations that in principle place limitations and oversight requirements on unfounded clinical applications of stem cells, but the enforcement of such rules appears to be ineffective at present, given the continued online presence of multiple clinics in these countries at the time of this writing. In both Germany [50] and Japan [51], the priority afforded to physician discretion in the use of interventions that have not undergone thorough testing has created *de facto* loopholes in the medical laws of these countries that enable stem cell clinics to operate with relative impunity (although German authorities shut down the largest clinic in the country following a number of reports of serious adverse incidents, including a death). Enforcement has also been incomplete in the United States, where dozens of stem cell clinics operate in states on the southern border of the country, with ready access to partner treatment centers in Mexico [52] and the Caribbean [53], and an increasing number of clinics now claim to provide treatments domestically [24]. The situation in the US is further complicated by an ongoing legal challenge to the authority of the FDA to regulate the medical use of autologous stem cells, launched by the owner of a company selling an autologous stem cell product for orthopedic repair [54].

Marketing of pseudomedical stem cell applications

Companies engaged in the international marketing of stem cell interventions of unknown safety and efficacy have made widespread use of online communications, coupled with strategies adopted designed to create a veneer of scientific credibility and deflect criticism, or alternatively to establish their stem cell treatments as a naturalistic "alternative medicine."

A number of prominent stem cell clinics seek to portray themselves as cutting-edge, scientifically sound institutes, which have simply foregone the customary process of rigorously testing products and treatment protocols in advance of commercialization, so as to maximize access or enable lower costs to patients. This strategy typically involves the presentation of various tokens of scientific credibility or

regulatory approval, which may include lists of publications and poster presentations by authors associated with the company, or by unrelated groups; patents and patent applications; disclaimers that treatments are experimental and results may show inter-individual variation (which may be reinforced in informed consent documents that paradoxically offer greater protections to the provider than to the patient); certifications of aspects of the business not directly related to the delivery of treatment; registration of clinical trial protocols for currently marketed interventions on public databases; establishment of non-profit foundations; enrolment of scientists and physicians to serve on advisory boards; claims of association or collaboration with prominent research and/or medical organizations; substitution of patient testimonials and speculation in lieu of data from rigorously designed clinical studies; and selective reference to uncritical media accounts. Examples of such marketing tactics are too numerous to list in detail; interested readers are directed to examine the corporate websites cited in this review. It should be noted that many legitimate biomedical companies engage in practices superficially similar to many of the above. The critical distinguishing criterion, however, remains whether a given organization sells treatments directly to patients and consumers for profit in the absence of rigorous and compelling evidence of safety and efficacy.

A second characteristic of companies marketing treatments for conditions that have not been scientifically shown to respond to stem cell interventions is the resort to distractive claims in defense of their unorthodox business practices. This can take the form of allegations of conspiracy on the part of the drug industry, the medical establishment, the mainstream media, regulatory authorities, and even other stem cell researchers, intended to forestall or prevent the acceptance of stem cell therapies out of fear of that it will damage business or funding models. Such claims have been made prominently by organizations such as the International Cellular Medicine Society [55], a not-for-profit organization established by the owner of the for-profit stem cell company Regenerative Sciences, and the Repair Stem Cell Institute [13], an online resource established by the primary financial backer of TheraVitae, a company that marketed stem cell treatments for cardiovascular diseases in Thailand. A small number of patient organizations, notably the Stem Cell Pioneers, have echoed these allegations regarding the suppression of effective stem cell therapies.

In addition to insinuations of conspiracy, stem cell treatment centers have also used legal tactics to silence criticism. The XCell-Center based in Köln and Düsseldorf, Germany, threatened to take legal action against the German Society for Neuroscience as well as an individual German neurologist following public statements questioning the scientific rationale behind their use of autologous bone marrow in the treatment of multiple sclerosis, spinal cord injury, autism, ALS, Parkinson's Disease and Alzheimer's Disease, among others (personal communication). As described above, the US-based company Regenerative Sciences has filed multiple unsuccessful complaints against the FDA, alleging that the agency was operating beyond its jurisdiction in requiring the company to pursue regulatory approval for their autologous stem cell product prior to marketing [56]. Investigators studying the phenomenon surrounding the commercialization of unproven stem cell treatments must take great care in archiving all referenced data, as much information is only published in electronic form and may be changed by the company operating a website in order to extinguish prior claims.

Some companies marketing unestablished clinical uses of stem cells take the contrary approach of portraying their stem cells as natural, integrative or holistic medicine [19]. This practice alludes to the supposedly harmless and harmonious nature of living cells, and may be marketed in conjunction with other unorthodox healthcare practices, such as acupuncture [57], homeopathy [58], qi gong [59], herbal remedies [60], astrology [61], or ayurveda [62]. In this marketing strategy, less effort is made to establish the scientific *bona fides* of a given treatment, while more emphasis is placed on the safe and natural quality of living cells, or the ancient roots of a given therapeutic approach (some of which refer as far back as to ancient Egyptian papyri or the Kama Sutra [63]). One clear historical antecedent for the purported use of living cells or tissues in alternative healthcare is the *Frischzellen* ("fresh cell") treatments promoted by Paul Niehans in Switzerland in the first half of the 20th century, in which lyophilized cells or tissues from animal sources were claimed to exert medical or rejuvenating effects on injection into human patients (for a brief review, see Reference 64). As with enterprises seeking to maintain an appearance of scientific credibility, companies that sell untested and unregulated products containing living cells do their patient-customers a disservice, and potentially put them at risk, by making claims of medical efficacy for stem cells in the absence of a solid evidentiary foundation.

Case study: commercialization of stem cell treatments for ALS

A closer examination of a number of companies marketing stem cell treatments for a specific condition — amyotrophic lateral sclerosis (ALS; also referred to as motor neuron disease) — can provide a more detailed understanding of the scale of the industry and its operating tactics. ALS is a progressive neurodegenerative disease of poorly constrained etiology, in which the degradation of motor neurons leads to increasing debility and death, typically within 3–5 years after diagnosis [65]. The disease affects mainly patients over the age of 40, and appears to be multifactorial, with several dozen of single nucleotide polymorphisms (SNPs) showing associations in patient subpopulations suffering from the sporadic form of the disease [66]. The current medical consensus is

that ALS is not curable at present, although symptomatic relief and delay of disease progress have been achieved through the use of the FDA-approved medication, riluzole, and physical therapy [67]. In 2009, the US-based biotechnology company Neuralstem received FDA approval to launch a Phase I clinical trial of the safety of neural stem cell injections in the treatment of ALS in conjunction with Emory University [68].

The poor prognosis and lack of treatment options for this disease appear to have made it a popular target condition for businesses selling unregulated stem cell applications. Companies located in the United States, Mexico, Russia, Germany, India, and China all advertise the use of stem cells to treat ALS, typically with weak and subjective claims of improvement. The XCell-Center in Germany, for example, while insisting that its approach is focused on reducing symptoms and slowing the consequences of the disease, that "Improvements were reported in 50% of the patients" [69], based on a sample cohort of 32 patients , do not indicate how many ALS patients in total have been treated. An independent follow-up by the watchdog group ALS Untangled of ALS patients who had received injections at XCell in contrast found that only one of three patients studied showed any benefit, and stated that, "Nothing useful can be concluded from the flawed ALS pilot data that are presented; the positive effects reported are very likely nothing more than a placebo effect ..." [70].

Beike Biotechnology, a major stem cell provider and patient recruitment service based in Shenzhen, China, which primarily markets allogeneic umbilical cord blood-derived mesenchymal stem cell treatments, similarly does not make curative claims on its website, but links extensively to an affiliated website, China Stem Cell News [34], which was set up to host selective anecdotes and testimonials from foreign patients who had received stem cell injections in Chinese hospitals. In its Patient Information Guide Summer 2010 [71], the company indicates that it has treated 458 ALS/motor neuron disease patients; it has published no articles on its ALS treatment protocol in an international scientific or medical journal to date, and has not registered any clinical trials for this procedure in a public database, or on the list of ostensible clinical trials it maintains on its website [72].

Several American companies, including Stem Cell Rejuvenation Center and StemProCell, now claim to treat ALS with stem cells domestically, without requiring their patients to travel overseas as has traditionally been the case in "stem cell tourism." These companies assert their practices are legal based on the dubious reasoning that they use autologous, minimally manipulated adipose-derived stem cells, reminiscent of the claims made in Regenerative Sciences' failed case against the FDA. This logic appears to neglect the separate requirement under CFR Title 21 Part 1271, "Human Cells, Tissues, and Cellular and Tissue-based Products," which indicates that such products must also be functionally homologous, not merely minimally manipulated, to be exempt under the law [73]. Neither company proposes any mechanistic rationale by which adipose-derived cells might specifically affect ALS, relying instead on testimonials and links to unrelated studies and media reports. Interestingly, the Arizona-based Stem Cell Rejuvenation Center, advertises one of the least expensive procedures among all companies publishing their fee schedules (see Table 1), suggesting that the explosive growth of the industry may have triggered price competition.

The Integra Medical Center in Nuevo Progreso, Mexico [57], presents a more holistic appearance in its description of its ALS treatment, which appears to involve the use of "placenta stem cells" in combination with acupuncture. The rationale is based on allusions to the Niehans *Frischzellen* therapy, concepts from traditional Chinese medicine, and unreferenced assertions about the biologic properties of human placenta, while efficacy is suggested primarily by a collection of video testimonials purportedly by satisfied patients.

Other treatment centers in Russia, India, Thailand, and the Seychelles advertise a broad range of different stem cell types (see Table 1), while resorting to similar marketing tactics to those described for the companies above. With the exception of Beike Biotechnology, none of the companies reports the total numbers of patients treated, making it difficult to estimate the total population of ALS patients that has undergone a stem cell intervention in an unregulated setting (and there is the additional problem of the lack of verifiability of figures self-reported by unregulated clinics). One common characteristic of all the companies sampled is the paucity of scientific evidence for safety, efficacy and indeed plausibility of their stem cell-based approaches; speculation, anecdote, media reports and patient accounts are used instead as a rhetorical substitute for scientific evidence. Interestingly, many of the companies operate openly in countries with established laws governing the clinical use of human cellular products, such as the United States, China, and Thailand, suggesting that enforcement even in these jurisdictions remains incomplete. In Germany, the current medical law apparently allows for a high degree of physician discretion in the administration of experimental treatments [50], while in India a set of guidelines proposed by the Department of Biotechnology nearly five years ago has failed to pass into law, rendering enforcement effectively impossible [74].

Challenges in regulation and patient education

As can be surmised from the above, and from the sheer scale of the industry in terms of revenues and numbers of patients treated, regulation has been proven only marginally effective to present. While the problem appears to have been eradicated locally within a number of countries, such as the UK and the Netherlands, the shutting down of a clinic in one jurisdiction

Table 1 Companies marketing stem cell treatments for amyotrophic lateral sclerosis (ALS)*

Name	Location	Cell type used	Delivery method	Cost
Beike Biotechnology	China	Allogeneic umbilical cord blood-derived stem cells (Beike also uses umbilical cord- and autologous bone marrow-derived stem cells)	Multiple (IV, lumbar puncture)	$26 300 USD for initial six injections
Chaitanya Stem Cell Therapy Center	India	Autologous bone marrow; Fetal stem cells	Intrathecal/intralesional injection	$6 000–$12 000 (bone marrow); $16 000 (fetal)
EmCell	Russia	Fetal stem cells	Not listed	Not listed
Integra Medical Center	Mexico	Placenta stem cells	Implantation in "different areas according to the patient's condition"; often in combination with acupuncture	Not listed
Nova Cells Institute	Mexico	Autologous bone marrow-derived stem cells	Not listed	Not listed
Stem Cell Rejuvenation Center	USA	Adipose-derived stem cells	Multiple (IV, in situ, IM, intranasal)	$8 750 USD
Stem Cells 21	Thailand	Adipose-derived stem cells	IV/IM injection	$18 000 USD
StemProCell	USA	Adipose-derived stem cells (processed using Adistem system)	Not listed	Not listed
Tissü	Seychelles	Mesenchymal stem cells	IV injection	Not listed
Wu Stem Cells Medical Center	China	Neural stem cells	Multiple (lumbar puncture, intracerebral injection)	Not listed
XCell-Center	Germany	Autologous bone marrow-derived cells	IV injection co-administered with mannitol	7 995 euros (adult); 9 000 euros (child)

* All data are taken from website and patient information resources published by the companies listed. All data reflect claims made as of March 13, 2011. Website data are archived using SiteSucker software ver 2.3.2. Abbreviations: IV = intravenous; IM = intramuscular.

frequently results only in its relocation to a second, less actively regulated locale. XCell-Center has its roots in the Netherlands, but after a tightening of the relevant Dutch medical law, moved to neighboring Germany to take advantage of its more advantageous legal climate. The German legislature has since revised the law, the amended version of which will go into effect in late 2012 [50]. In early May 2011, XCell-Center ceased its operation in Germany [5]. Multiple companies located in states along the southern border of the United States have skirted regulation by recruiting patients domestically and sending them for treatments in Mexico or Caribbean nations nearby. In Asia, it was recently reported that the major Korean biotechnology firm RNL Biosciences had been engaged in surreptitious marketing of stem cell treatments, sending as many as 10 000 patients to private hospitals in Japan and China over the course of several years [75].

Confusion over governmental stances toward stem cell companies offering untested treatments has also been a problem, particularly in Asia, where public investments into stem cell research have frequently emphasized application in advance of basic science [76]. In Thailand, the national Board of Investment recognized TheraVitae as a leading [77] innovator even as the Thai Medical Council and FDA were seeking ways to develop stricter regulations on the industry. In China, Beike Biotechnology established partnerships with multiple provincial, municipal, university and military hospitals [71], and claimed that it had received the equivalent of more than $6 million in government grants as of 2009. In India, Geeta Shroff's NuTech MediWorld clinic has enjoyed public support from senior government officials, at least one of whom is reported to have received her proprietary human ES cell treatment [74]. This lack of uniformity and clarity in governmental positions has resulted in not only the continued ability of companies evidently in violation of local laws to remain in business, but may lend an appearance of legitimacy that could influence the decisions of patients considering such treatments.

Given the profitability, mobility, sophistication, and resourcefulness of companies engaged in the sale of stem cell injections of unproven safety and efficacy, it does not appear that it will be possible to achieve globally effective regulatory control over this problem any more than it has been to the wider industry surrounding unorthodox healthcare approaches. It would appear to be in the best interests of individual countries to limit the ability of clinics to deliver treatments promising egregiously implausible results on a domestic basis, not only for the health, financial security, and emotional wellbeing of their citizens, but also as a means of sustaining their reputations as world-class biomedical research powers. The ability of companies to operate with apparent impunity within the borders of leading nations such

as China, Germany, and the United States may have the additional effect of encouraging patients to undergo treatments they would consider more carefully about if offered in a less well-developed context, and may adversely affect the reputation of the scientific and regulatory climates in these places as well. Appropriate regulatory pathways and enforcement are hallmarks of successful environments for innovation, and scientists and physicians engaged in research and development in biomedicine need to communicate and work with competent authorities to ensure the quality and safety of treatments that may emerge from their efforts.

Communication with prospective patients and other stakeholders is perhaps even more important than regulation. A number of organizations engaged in stem cell research or regenerative medicine have issued white papers [42], patient handbooks [78], and public statements on the risks and concerns surrounding the unregulated clinical use of stem cells [41]. Disease advocacy groups have likewise produced educational materials [79–81], checklists, and alerts [82] regarding groundless claims relating to their conditions of interest. Major media organizations have produced critical print [83], and televised [84] reports in recent years, which have shed light on some of the more dubious practices, but according to one recent analysis, the overall trend in the tone in reporting stem cell travel has been increasingly positive [36]. Much work remains to be done to gain wider public understanding of the current state of stem cell science, and the challenges that lie ahead before their clinical application can be achieved in a responsible, ethical and scientifically rigorous manner.

The research and clinical communities can also do much to help raise awareness and skeptical consideration of claims by directly addressing the evidentiary basis and scientific plausibility of claims made by commercial vendors of untested stem cell products, and by working closely with competent authorities to ensure that this technology is shepherded into clinical use and introduced into the market in an appropriate and circumspect manner. The promise of stem cells in medicine remains great, and clinical trials now underway around the world are showing promise for the next generation of cell-based therapies, which may usher in a new, scientifically sound and clinical meaningful paradigm in the treatment of a range of currently intractable conditions.

Executive summary

- The marketing of untested and under-regulated stem cell products has developed into a global industry involving hundreds of companies
- Private clinics and physicians around the world claim to use stem cells of various types to treat an extraordinarily broad range of medical and quality of life indications
- Such stem cell clinics operate in regulatory gaps, or even in direct violation of local laws and guidelines; many are based in advanced economies
- Bringing this industry under responsible oversight will require concerted efforts on the part of regulatory authorities, medical and scientific organizations, as well as education and engagement of patient groups

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