

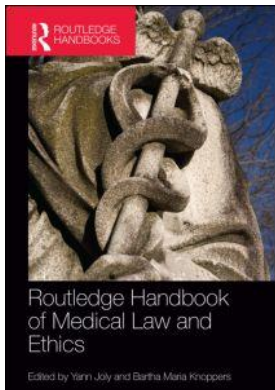
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The domestication of stem cell tourism

Douglas Sipp

24.1 Historical background of stem cell marketing

The rise of international marketing for putative stem cell products and procedures, commonly referred to as ‘stem cell tourism,’ is a well-documented phenomenon that dates back to the early 2000s (Lau *et al.* 2008; Kiatpongsan and Sipp 2009; Regenbergs 2009; Ryan 2009; Sipp 2011a). The modern commercialization of unregulated cell or tissue biologics traces its origins to transplants of fetal brain or adrenal tissue for neurological diseases in the 1980s and 1990s (LeVay 2008). Further, commercialization practices gained widespread popularity in Europe and in the United States where xenogeneic transplants of lyophilized cells, tissues, or extracts harvested from sheep, rabbits, goats, and monkeys, and described variously as *Frischzellen* (fresh cell), live cell, or Sicca cell therapy, began in the 1920s and continues today (Last 1990; Van Dyke *et al.* 1990). These nascent examples demonstrating the unregulated sale of cell- or tissue-based products displayed many of the hallmark features of present-day stem cell marketing: extraordinary claims of medical efficacy or rejuvenating power of living cells or cell extracts, widespread use of media innovations, and mention of required overseas travel for patients. In one well-known example, John Brinkley, known as ‘the goat gland doctor,’ pioneered the use of commercial radio in the 1920s, and later established the first ‘border blaster’ station in northern Mexico to reach American listeners while evading federal laws (Brock 2008). Despite the popularity of Paul Niehans’ ‘fresh cell’ approach across German-speaking Europe, and a brief public fascination with fetal tissue transplants in Asia and Latin America in the 1980s, the demand for cell and tissue medicinal products has historically been a niche market.

Unlike its antecedents, however, contemporary stem cell tourism has developed into a global industry. It comprises hundreds of companies across dozens of countries offering supposed ‘stem cell’ products and services advertised for medical, nutritional, cosmetic, anti-aging, and veterinary applications; some websites list over 100 distinct ‘treatable conditions’ (Repair Stem Cell Institute (RSCI) 2013). Consensus among the scientific and medical communities remains that stem cells, of any kind, have only been shown to be safe and efficacious for non-experimental use in the treatment of hematologic cancers and other blood/immune diseases using hematopoietic stem cells (HSCs), and the repair of corneal damage using limbal stem cells (Daley 2012). In both of these stem cell-based treatments, the demonstrable therapeutic effect is attributable to

homologous use, i.e. the cells function as they ordinarily do in the body (HSCs generating blood cells, limbal cells generating corneal epithelium). In contrast, many businesses that advertise putative stem cell interventions make claims about ‘non-homologous’ uses, such as HSCs to generate heart tissue, or of mesenchymal stromal cells – which ordinarily give rise to bone, cartilage, and fat cells – in the repair of the nervous system. Additionally, stem cell clinics often advertise products that are clearly manipulated and capable of altering the biologic activity of cells, such as through long-term culture or treatment with exogenous growth factors or hormones. (The concepts of ‘homologous use’ and level of *ex vivo* ‘manipulation’ have legal implications in the United States and other countries, as described below.) The operation of such clinics in extra-legal settings further places them beyond effective oversight or independent scrutiny. As a result, a number of companies and individuals have been found mislabeling slurries of mixed tissues (Jandial and Snyder 2010), animal cells (Trossel 2010), dead cell fragments (60 Minutes 2012), and even inert vehicles such as saline for direct sale to patients (*Campbell v. Immunosyn Corporation et al.*, case no. 692711 (complaint filed in 2009, but case has yet to proceed) (Texas Southern District Court)). Notwithstanding the lack of evidence or scientific consensus on the safety and utility of these companies’ medical offerings, and the great potential for exploitation, fraud, and abuse, the industry continues to boom.

24.2 Convergent factors

Resistance to human embryonic stem cell (hESC) research on religious or ethical grounds triggered an immediate search for alternatives, prompting strong enthusiasm among some groups for the development of adult (somatic) stem or progenitor cells, such as umbilical cord blood- or adipose-derived mesenchymal multipotent stromal cells (commonly referred to as mesenchymal stem cells, or MSCs), olfactory ensheathing glial cells, and endothelial progenitor cells (Prentice 2003; Prentice and Tarne 2007; Focus on Family 2009). This enthusiasm for adult stem cells as a viable clinical alternative to hESCs led in some cases to a misunderstanding (and occasionally to deliberate misrepresentation) of the clinical utility of stem cell-based interventions, spurring demand in advance of evidence to suggest their safety and efficacy (Sipp 2013a).

The reluctance or refusal to fund hESC research in various national jurisdictions, including, importantly, the US (for eight years, the National Institute of Health (NIH) limited funding for such research to a small number of preexisting cell lines), motivated numerous Asian countries to invest heavily in stem cell research of all kinds. Notable in this regard were China, South Korea, Singapore, Thailand, Taiwan, and India. The failure of the US to capitalize on its traditional strengths in biomedical research and development in this area was apparently perceived as an opportunity for such countries to gain a foothold, or a lead, in the development of advanced biomedicine, at a time when much of East Asia was seeking to diversify away from heavy industry and manufacturing (Sipp 2009a, 2009b). Additionally, several countries in the region, of which Thailand, India, and Korea are prominent examples, simultaneously invested in establishing ‘medical tourism’ as an important economic sector. In the early days of unchecked optimism about the broad-spectrum clinical efficacy of stem cells, government agencies directly supported this investment, or promoted the operation of private companies that would come to be recognized as stem cell tourism operators (Thai Board of Investment 2005; Korea Tourism Organization 2013).

The presumption of efficacy was further amplified by a trend commonly witnessed in areas of leading-edge science: hyperbolic reports in the media and overenthusiastic speculation on the part of scientists. Media coverage of both stem cell science and of patient travel to obtain putative stem cell therapies has also contributed to uncertainty over the safety and clinical benefit of

stem cell interventions. Examples of major print, broadcast, and online media outlets running stories suggesting that stem cells are ‘the future of medicine’ or ‘a miracle’ are too numerous to list. Media coverage of direct-to-consumer marketing of stem cell-based interventions has been remarkably positive. Analyses of English-language (Zarzeczny and Caulfield 2010) and Chinese-language (Ogbogu *et al.* 2013) media reports on this phenomenon suggest that the trend has been increasingly to cast these procedures in a sympathetic light, and frequently to assist in fundraising for specific patients to travel overseas.

Much has been written about the pressures on basic scientists to suggest applications for their findings even at the earliest stages of research (Fang and Casadevall 2010; Levenson 2013). This is certainly the case in stem cell biology, which has become an area of science used as a yardstick of national research competitiveness, as evidenced by reports that the US had fallen behind Asia in the stem cell race (Einhorn *et al.* 2005), or that EU prohibitions on hESC patenting would hamper the ability of European labs to keep up (Kemp 2011). In 2013, an international group of scientists published a commentary on how the pressure to rush fundamental science into translational research has led the state to overestimate clinical development in stem cells, fueling patient demand, public urgency, and the premature marketing of stem cell ‘cures’ (Bianco *et al.* 2013). Stem cell clinical studies, many of which are conducted by academic or government organizations with little experience in conducting clinical trials, have been found to use potentially misleading language suggesting ‘therapeutic intent’ to describe research protocols much more frequently than comparable studies involving small molecule drug candidates (Scott *et al.* 2010).

The system’s vulnerability to abuses in scientific integrity and quality assurance is also highlighted in the marketing practices of many stem cell clinics. The rise of ‘predatory’ publishers has made it simple to publish superficially peer-reviewed articles describing poor-quality or overly-speculative studies that may be indistinguishable from legitimate science to non-specialist readers (Beall 2012). Patent filings and penny stock listings are also readily obtained and useful in creating a veneer of legitimacy. Surprisingly, registration of clinical trials, particularly those using cell types such as MSCs, with which the drug regulatory authority may have some familiarity, is also apparently straightforward; numerous companies have successfully registered studies for single indications while actively marketing identical stem cell treatments for a myriad of other medical conditions. In 2011, for example, the US Food and Drug Administration (FDA) issued a warning letter to TCA Cell Therapeutics for treating multiple patients outside the indications listed in their five registered clinical trials (FDA 2011a). Groups of physicians engaged in the marketing of unapproved stem cell interventions have banded together to form societies which lobby for the deregulation of stem cell biologics, issue accreditations, and share business practices (Kuehn 2009). Meanwhile, individual practitioners may seek membership or submit presentation abstracts to societies not typically associated with the commercial promotion of spurious stem cell interventions, which can then be used in marketing as tokens of credibility.

One unifying thread among these practices is the reliance on the Internet as a relatively unregulated, inexpensive, and effective medium for targeting marketing messages to patients. The nature of online business provides the low startup and operating costs, mobility, anonymity, extraterritoriality, and broad reach that enable clinics located even in poorly resourced countries to communicate directly with users. Users search for combinations of keywords relevant to their conditions that are supported by search engine optimization and paid placement of advertisements through programs such as Google’s AdWords. The Internet has also had an undeniably positive effect on patient empowerment and activism, allowing individuals to educate themselves about their medical conditions and treatment options, and to network with others affected by the same or similar diseases. However, it has also served as an inexpensive and extraordinarily effective marketing and recruitment forum for predatory stem cell clinics (Ryan *et al.* 2009).

Patient communities and blogs are a rich resource of information on individuals' disease status, and have occasionally been aggregated by clinics for use as a promotional tool.

Normalization of medical travel, lack of adequate health care insurance (particularly in the US), and generalized frustration with the medical system have also provided fertile soil for the growth of the illicit stem cell industry. Medical tourism, as mentioned above, has become an important sector in many developing economies, and patients in rich countries are accustomed to the idea that affordable quality care may be available beyond their national borders. Millions of people in the United States still have no or inadequate medical coverage, which, coupled with unusually high healthcare costs, fuels public disaffection and willingness to travel overseas for care. However, while potentially improving access, affordability, and speed of treatment, this phenomenon is not without its issues. It may be difficult for seriously ill patients to travel, which can leave patients without emergency medical care or legal recourse following an adverse event, and may make it difficult to access or retrieve medical records post-treatment (Turner 2010).

The growing popularity of so-called complementary and alternative medicine (CAM) (also referred to as 'integrative medicine') is a symptom both of dissatisfaction with conventional medicine, and preferences for minimally invasive, 'natural,' or holistic approaches to care (Eisenberg *et al.* 1993). Many businesses engaged in the sale of ostensible stem cell products offer combinations of stem cells with acupuncture, traditional folk medicine, homeopathy, or other alternative modalities (Sipp 2011b). The marketing of herbal or nutritional supplements purporting to boost stem cell function or increase the number of stem cells circulating in the bloodstream has also grown over the past decade.

The religious underpinnings that motivated further research into hESCs as therapeutic alternatives for adult stem cells illustrate how ideology can play an important part in shaping public perception. A small but vocal movement to rally opposition against the notion that autologous stem cells can be regulated as biologic drugs has arisen amid a more general opposition to government regulation of healthcare. The latter was first organized by free-market think-tanks such as the Heritage Foundation, Manhattan Institute, and Cato Institute in alliance with groups of physicians seeking to defeat federal oversight and disaffected patient groups (Sipp 2013a).

It is clear from this brief overview of contributing factors that the rise of direct-to-consumer stem cell marketing seems overdetermined nearly to the point of inevitability. The convergence of social, economic, political, legal, and ideological undercurrents led first to the emergence of clinics located on the fringes – in medical tourism hubs, island resorts, and towns bordering major developed markets. In the following section, I review what appears to be the largest growth area for the industry in recent years. Using the United States as the leading example, I discuss the emergence of scientifically dubious stem cell clinics practicing regulatory brinkmanship or openly defying the law in developed nations with well-established regulatory infrastructure.

24.3 Reborn in the USA

Although international travel is now considered the hallmark of 'stem cell tourism,' one of the first documented 'stem cell' clinics (Biemark International, which claimed to use umbilical cord blood-derived stem cells in the treatment of neurological conditions) was based within the United States and primarily targeted American patients (Zaremba 2005). After a federal investigation for medical fraud, the proprietors of the company fled the country. They subsequently established a similar company, Advanced Cell Therapeutics, which operated briefly in Europe and later in South Africa, as well as a separate outfit, Tissü, in the Seychelles. The globetrotting impunity of BioMark's owners – a South African man and his American girlfriend – highlights

not only the difficulty in regulating international businesses, but also the ready portability of the business model.

Many other early businesses engaged in the promotion and sale of unproven or under-regulated stem cell interventions, which have also been closely linked to individuals or companies from the United States. Theravita, a Thai-Israeli joint venture based in Bangkok, was established by an American businessman and marketed an unvalidated transplant technique introduced by an academic cardiologist based in the US. Theravita also served as the model for one Florida cardiologist who established a company, Regenocyte, that sent patients to a partner stem cell clinic in the Dominican Republic; he later lost his medical license when two patients he treated domestically in the US died after or during procedures (Freeman 2013). Beike Biotechnology, a large Chinese public-private company based in Shenzhen, served as a cord blood bank and a recruitment and referral service for patients seeking stem cell injections in China. It was established by a Chinese scientist-entrepreneur and an American businessman who was previously reported to have been involved in trafficking and harvesting organs from executed prisoners (Spencer 2005; BBC Panorama 2009). A Ukrainian scientist and an American businessman/artist jointly operated the Institute of Regenerative Medicine, a Bahamas-based clinic, and also putatively used fetal cells from Eastern Europe (Thompson 2006). Medra was a clinic located in the Dominican Republic, but was owned and operated by a California psychiatrist claiming to use fetal stem cells imported from Eastern Europe to treat serious medical conditions (BBC Panorama 2009). (Medra has since been renamed Stem Cell of America and now sends its patients to Mexico.) The Institute for Cell Medicine in Costa Rica (now the Panama-based Stem Cell Institute), which advertises interventions using various somatic stem cell types for the treatment of neurological and autoimmune diseases, was launched by a US entrepreneur in close collaboration with the publicly traded stem cell company Medistem, a company of which he was also chairman. Clearly, from its earliest days, the 'stem cell tourism' industry has not been limited to locally owned companies in developing economies with poorly developed regulatory systems.

The opening of Regenerative Sciences by a Colorado-based physician, businessman, and activist marked a turning point in stem cell tourism, from clinics relying on outbound travel to clinics operating within US borders. Regenerative Sciences was accompanied by the establishment of the International Cellular Medicine Society (ICMS) (originally named the American Stem Cell Therapy Association), a coalition of like-minded practitioners that actively lobbied for the deregulation of autologous stem cell products. For example, members of the ICMS Board are required to affirm statements that appear to be in direct contravention of current federal regulations:

... minimally culture expanded stem cells are 1). Part of the practice of medicine and used as part of a physician practice in one state and through the state practice of medicine, 2). Do not constitute the creation of a new biologic drug or product that would fall under any part of FDA regulation on new drugs or biologics and 3). Exempt from any US Food and Drug Administration regulations ...

(International Cellular Medicine Society 2013)

In 2007 Regenerative Science began marketing a processed autologous stem cell product under the trade name Regenxx, and the following year received an untitled letter from the FDA informing them that they appeared to be promoting the '... use of mesenchymal stem cells under conditions that cause these cells to be drugs ...' under relevant federal law. This prompted a series of suits and countersuits between Regenxx and the FDA that were decided by the District Court in 2012, and are currently under appeal (Sipp and Turner 2012).

The law in question is the *Code of Federal Regulations* (Title 21, Part 1271), which defines the regulations over human cell and tissue products (HCT/P). These products are broadly defined as any human cell, tissue, or derived product that is introduced into interstate commerce and that meets any one of the following criteria: (1) more than minimally manipulated; (2) intended for non-homologous use; (3) systemic in effect; or (4) shows metabolic activity. Important exceptions to these rules include blood and blood products, vascularized tissues or organs, human reproductive cells intended for immediate transfer to an intimate partner (all of which are regulated separately) and, importantly, establishments that harvest ‘HCT/Ps from an individual and implants such HCT/Ps into the same individual *during the same surgical procedure*’ (*Code of Federal Regulations*, Title 21, Part 1271) (emphasis added by author). For its part, Regenerative Sciences insisted that the harvesting and transplantation of autologous stem cells should be considered part of medical practice, a state-regulated activity in the US, rather than the federally regulated manufacture of a biologic drug.

US-based clinics were quick to note and take advantage of the same-surgical-procedure exemption. In effect, the exemption removes from federal oversight the marketing of stem cell-based interventions in the absence of rigorous evidence of safety, purity, and efficacy that would typically be required of a drug, medical device, or biologic. Regenerative Sciences itself was one of the first to exploit this regulatory gap, introducing a number of alternatives to its cultured cell product (Regenexx-C) that are delivered in what is described on the company website as the same surgical procedure.

The fields of aesthetic plastic surgery, orthopedic repair, and anti-aging medicine were quick to awaken to the possibilities of selling weakly regulated autologous stem cell interventions on a direct-to-consumer basis without the need to go through the time-consuming, expensive, and uncertain validation process required for other medicinal products. One of the most popular forms of autologous cell treatments available is a combination procedure that harvests a small amount of fat from the patient; this fat is then spun in a centrifuge to obtain the MSC-rich stromal vascular fraction, which is then re-injected into another site in the same patient’s body for medical or cosmetic purposes. The scientific evidence supporting the efficacy of such procedures remains equivocal at best, and the absence of accepted standards of care makes it certain that there is wide variability in clinical practices. Indeed, the American Society of Plastic Surgeons and American Association of Aesthetic Plastic Surgeons have jointly issued a position statement that, based on current scientific evidence available, it is premature to market stem cell interventions (Eaves *et al.* 2011). Similarly, the American Association of Orthopaedic Surgeons (AAOS) maintains that ‘stem cell procedures in orthopaedics are still at an experimental stage’ (AAOS 2007).

Therapeutic claims about autologous stem cells harvested and transplanted in the same surgical procedure are not limited to cosmetic surgery and joint repair. A growing number of domestically operating clinics now claim to treat more serious medical conditions on an experimental, but for profit, basis. In past years, a small number of naturopathic clinics made similar claims for putative stem cell products, but this practice has now moved into mainstream medicine. The Cell Surgical Network (2013) established by the California Stem Cell Treatment Center now has practice affiliates in Hawaii, California, Arizona, Nevada, Colorado, Texas, Iowa, Illinois, Indiana, Mississippi, Florida, Georgia, North Carolina, New York, Connecticut, and Massachusetts, offering experimental same-day injections of autologous cells for neurologic, cardiovascular, urologic, autoimmune, ophthalmologic, and orthopedic conditions, as well as hair restoration. Regenerative Sciences has also introduced a Regenexx Provider Network licensing program, and a number of companies have begun to offer courses in stem cell harvesting and transplantation.

One increasingly popular trend in clinics both overseas and in the US is to provide services as part of ‘clinical trials’ or ‘on an experimental basis,’ so that patients who wish to participate in ‘research’ must pay the costs. By wording websites and informed consent documents in ways that indemnify the providers not only against unforeseen adverse effects but also against lack of efficacy, these ‘pay-to-participate’ marketing schemes blur the already fuzzy lines between experimentation and care in this area of biomedical development, and place an undue burden on patients willing to volunteer as test subjects at some physical risk to themselves (Sipp 2012). Conservative organizations have begun to promote the notion that the regulation of stem cell products is overly stringent, and safety studies should be sufficient to bring products to market after surveillance and outcome databases can be used to determine efficacy (Gottlieb and Klasmeier 2012). If enacted, these requirements would seem to achieve the same end result: transferring the financial responsibility for research costs from for-profit companies to vulnerable patients.

In addition to the commercialization of procedures with therapeutic intent, many companies sell nutritional supplements or cosmetics alleged to boost the function of the body’s endogenous stem cells. Although the FDA regulates both supplements and cosmetics, such products undergo a much lower level of scrutiny. The *Dietary Supplements Health and Education Act* of 1994 placed severe limits on the FDA to require premarket safety and efficacy testing for nutritional supplements, so long as their makers confine their labeling to so-called ‘structure/function’ claims and disclose that the product has not been reviewed by the FDA (Hurley 2007). Thus supplement makers are at liberty to assert their products, for example, ‘support liver function’ or ‘enhance metabolic activity’ by ‘stimulating stem cells,’ but cannot claim to treat, cure, or mitigate any disease. One of the most popular such products, StemEnhance, is sold as part of a distributed marketing scheme and claims to have earned more than \$1 million USD in revenue in its first month on the market (although it appears that a very similar product, Cell Enhance, created by the same individual, was on the market for more than a decade prior to its rebranding). Several individuals affiliated with medical stem cell clinics have also developed proprietary brands of stem cell supplements (such as Stem-Kine and Regenexx). To date, the FDA has not taken action against the manufacturer of a stem cell nutritional supplement.

Cosmetic manufacturers are also at much greater liberty in labeling their products than are makers of drugs and devices. The FDA’s primary role in the regulation of conventional cosmetics is monitoring for adulteration, misbranding, and post-market safety issues; premarket testing is not required, and claims are evaluated with an eye to whether they are likely to be more or less ‘exaggerated’ (Liang and Hartman 1999). With the advent of new bioactive cosmetic products (i.e. those products whose function is not merely to conceal or enhance superficial features, but to effect changes in some physiological process or function) are calls for the creation of a regulatory category between cosmetics and drugs, often referred to as cosmeceuticals. However, the law in this area remains controversial and unevenly applied. Thus sunscreens, antiperspirants, and antidandruff shampoos manufactured in the US are regulated as drugs, while topical theophylline and retinol can be sold as cosmetics (Elsner and Maibach 2005). Major cosmetics manufacturers use highly suggestive claims to boast the regenerative effects of the product or the inclusion of stem cells in their formulae. A subset of these products claims to use ‘stem cells’ from plant species, including edelweiss, bilberry, argan, butterfly bush, Echinacea, apple, and grape, among others, and typically places a strong emphasis on their supposed ‘natural’ and ‘rejuvenating’ properties. In 2012, the FDA issued a warning letter to L’Oréal over claims made about the properties of several of its products, the first such enforcement activity against a stem cell cosmeceutical (FDA 2012). Thus it appears that the majority of companies selling ‘stem cell’ medical treatments, nutritional supplements, and cosmetics have found exceptions, exemptions,

and lacunae within the law that enable them to operate with little fear of federal intervention and little need to support their claims with scientific evidence prior to (or after) entering the market.

Removing the necessity of overseas travel for patients seeking stem cell interventions has also had clear implications for the industry. On the positive side for consumers, the expansion of choices on the market, which now encompasses both foreign outfits and US clinics marketing 'same surgical procedure' transplants, appears to have brought about price competition, resulting in lower prices for consumers. This is a good thing overall, as even in the event that the products turn out to be spurious or inefficacious, the financial harm is mitigated to some extent. However, it must be noted that the economics of this industry remain poorly understood due to the lack of transparency and, paradoxically, a number of clinics now appear to be charging more than the former industry average of around \$20,000 USD per treatment (possibly seeking to differentiate themselves on the basis of 'quality' as reflected by price).

The downsides to the domestication of what was formerly a touristic phenomenon have been subtler, but perhaps over the long term more profound. The erosion of the scientific integrity of medical practice in the United States, as typified by the ascent of complementary and alternative medicine as independent modes of healthcare, and their increasing integration into mainstream practice and academia, is well documented (Chaterji *et al.* 2007; Gorski 2008). This appears to be a partial consequence of the deprofessionalization and subjection of healthcare to market forces over the past four decades. In free-market medicine, patients are free (as they should be) to make decisions about their treatment options. Likewise, providers are free (ill-advisedly) to make claims based not on scientific research, but 'whatever the market will bear.' A discussion of the perils of the free-market model for scientific integrity and progress in medicine is beyond the scope of this article, but excellent reviews of the subject from medical and economic perspectives are available (Relman 2007).

24.4 Regulatory responses

Despite the rapid ascendancy of stem cells across multiple pseudomedical product categories, the domestic healthcare and regulatory systems are not entirely defenseless against such unsupported claims and business practices. Since 2011, the FDA has stepped up its enforcement activities, conducting inspections and issuing a half-dozen warning letters to clinics and companies (Sipp 2013b). This regulatory response appears to have been timed not only to the growth of the domestic industry, but to the resolution of the *U.S. v. Regenerative Sciences* [2012] 878 F. Supp. 2d 248 case which, had it been decided in favor of the defendants, could have overturned the FDA's authority over a broad swath of cell biologics. State and federal law enforcement have also taken action against fraudulent stem cell claims. In 2011, two men in Nevada were charged with conspiracy to commit mail fraud and wire fraud over stem cell treatments that they had been marketing since 2005 (FDA 2011b); both entered guilty pleas in 2012. More dramatically, a group of people, including an academic researcher, involved in a fraudulent stem cell business exposed by the television news program 60 Minutes, were arrested and convicted for their parts in the scheme (US Attorney's Office 2012; Glenn 2013).

State medical boards could also potentially play an important role in reining in the more egregious claims of physicians advertising unproven stem cell treatments. To date, only the Florida Board of Medicine has taken disciplinary action, and then only after two fatal complications of stem cell transplants performed within the state (Freeman 2013). The failures of state medical board systems to discipline practitioners, even in cases of serious breaches of professional and ethical conduct due to lack of resources, fear of litigation, and unwillingness on the part of fellow

doctors to report their colleagues are not however limited to the area of stem cell marketing, (Eisler and Hansen 2013). Thus it appears unlikely that state boards will take action in any but the most serious and ironclad of cases. In the state of Texas, where the governor (himself the recipient of an unvalidated stem cell injection) prompted the State Medical Board to enact a rule protecting physicians from disciplinary action in the event that they deliver stem cells on an experimental basis, that likelihood would appear to be even lower still (Kaiser 2012).

The civil courts have been underutilized for litigation against stem cell companies and providers who have made ostensibly spurious or misleading claims. A group of Korean-American patients who were treated by clinics affiliated with Human Biostar, the US affiliate of Korean stem cell firm RNL Bio (now K-Stem Cell), filed suit against the company, alleging that it 'defrauded elderly Plaintiffs through false representations that experimental stem cell therapy ... would cure not only all known ailments, but would also reverse aging' (*Ben Hang Lee et al. v. Human Biostar Inc. et al.* (complaint filed in 2012, but the case has yet to proceed) (California District Court)). Several law firms are now actively soliciting plaintiffs for lawsuits against fraudulent stem cell clinics (Schmidt Firm LLP 2012) and even a potential class action suit against Lancôme for its promotion of misleading health claims associated with some of its 'stem cell' cosmetics (Blankinship 2013). But given the sophistication of the marketing claims for unproven stem cell products and interventions, frequently accompanied by disclaimers that they have not been reviewed by the FDA, they remain experimental. That is, such products and interventions offer no guarantee of safety or efficacy, and the widespread use of informed consent documents serve to indemnify providers against litigation and insulate them against malpractice claims. Therefore it remains to be seen whether courts will look on such suits favorably. The depiction of stem cell treatment as an area of complementary and alternative medicine may work to the advantage of providers, as it is more difficult to win malpractice cases against CAM practitioners, given their highly limited scope of practice and non-reliance on conventional standards of care (Jesson and Tovino 2010).

24.5 Conclusion

The United States and other countries have seen a stem cell invasion in recent years. If unsupported medical claims for stem cells are allowed to remain unchecked, it may have serious consequences not only for public health and patient safety, but for the future of legitimate stem cell research as well. Over the past half-century, American patients and consumers have grown accustomed to a market in which the safety and efficacy of medicinal products must be demonstrated prior to being approved for distribution. They are growing less accustomed, unfortunately, to the notion that medicine is not a business, but a profession guided by codes of conduct that prioritize patient care. Efforts to shift the oversight of these interventions from the stringent regulatory framework for cell biologics to the more liberally regulated practice of medicine reflect this new reality. Emphasis on freedom of choice resonates with patients, especially those with intractable conditions who may be disillusioned with the current system. However, many gloss over the basic guarantees of quality and reliability that make such freedoms worth exercising. It has been noted that the history of medicine, which until very recently has been unregulated with respect to premarket evidence of efficacy, is the history of the placebo: free markets are notorious for their inability to distinguish safe and effective products and services from ones that are merely safe and attractively presented. By making the case for clinical uses of stem cells through marketing pitches rather than rigorous and reproducible scientific studies, companies engaged in direct-to-consumer marketing of these interventions do their customers and the field a deep disservice.

The opening of the domestic market to companies that take shortcuts around the FDA regulatory pathway also leads to significant market distortion to the disadvantage of companies that seek to introduce products via the established route. Costs for the clinical development, testing, and authorization of a stem cell product for a single indication are estimated around \$100 million USD and take a decade or more to approve for commercial use. But when companies, clinics and individual providers are able to begin earning nearly instant profits, then clearly they will financially outcompete traditional companies at least in the near-to mid-term. Low startup and running costs as well as direct-to-consumer marketing that includes promotional texts, albeit it without promises or evidence of efficacy, have enabled companies to do so. The profitability of the direct-to-consumer stem cell marketing model is undeniable, and has not gone unnoticed within the industry – many companies with registered clinical trials now partner with clinics in neighboring countries to which they send patients who wish to buy into a research study as a paying subject (a practice that is typically not permitted in the US and which raises serious ethical issues). My future work will examine the serious issue of publicly traded companies that either engage directly in such practices or act as direct suppliers. For now, regulators and consumers must become more vigilant to the unsupported claims of medical utility among stem cell therapeutics if public trust in the field is to be maintained.

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