■ ANNOTATION

Rogue stem cell clinics

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Cell therapies hold significant promise for the treatment of injured or diseased musculoskeletal tissues. However, despite advances in research, there is growing concern about the increasing number of clinical centres around the world that are making unwarranted claims or are performing risky biological procedures. Such providers have been known to recommend, prescribe, or deliver so called 'stem cell' preparations without sufficient data to support their true content and efficacy.

In this annotation, we outline the current environment of stem cell-based treatments and the strategies of marketing directly to consumers. We also outline the difficulties in the regulation of these clinics and make recommendations for best practice and the identification and reporting of illegitimate providers.

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Introduction

Cell therapies have generated considerable interest as potential treatments to modify symptoms, or heal injured or diseased tissues. There is well-documented success for some forms of cellular therapy.[1,2] Blood transfusion was the first example of this form of treatment. Other early examples include split-thickness skin graft which transplants skin-derived stem cells, and bone-marrow transplantation which involves the grafting of true hematopoietic stem cells.[3] Substantial basic and translational work to has been done to develop opportunities for cellular therapies in musculoskeletal disease responsibly and rationally.[4-7] However, all stages of the ideal translational pathway whereby in vitro data are used to inform preclinical models, which later form a phase I/IIa first-in-man study and subsequently phase III clinical trials have not yet been completed for the regeneration of articular cartilage.[8]

Despite a considerable legitimate research effort, there is increasing concern about the range of unregulated and poorly characterized cell therapies being offered by some providers, often marketed as 'stem cells', with claims of efficacy and safety not founded on clinical evidence.[9,10] Some providers, motivated by opportunistic benefits and without regard to evidence-based patient care, promote unproven and expensive treatments that may offer little benefit, and even worse may pose large risks to the health of vulnerable patients.[11] Clinics and providers making unsubstantiated claims inadvertently discredit this important area of research and threaten to impede the progress of legitimate clinical translation by portraying an exclusively positive message, without providing a fair balance of the risks, benefits, and limitations.[12] There is an urgent need to raise awareness of discrepancies between what is being marketed and offered to patients and the clinical evidence and regulatory landscape for cell therapies. In this annotation, we draw on a growing body of literature describing the industry of entrepreneurial clinics focused exclusively on marketing cell–based therapies directly to patients.[13-15] We highlight a number of key challenges faced by those charged with regulating this industry.

The scope of the problem. Historically, the narrative of 'stem cell tourism' has involved travel to facilities located in countries such as China, India, and Russia[16-18] with the perception that these countries allow the providers of clinics to operate without rigorous regulatory oversight. While travel to international clinics still occurs, unproven cell therapies are increasingly being marketed directly to consumers in the USA and Europe.[19,20] As of May 2017, 432 distinct US businesses were selling 'stem cell' based treatments provided at 716 clinics, and this number appears to be rising rapidly.[21]Such companies are particularly widespread in certain states in the USA, with 67% of clinics located in California, Florida, Texas, Arizona, and Colorado.[13] Most clinics market cell preparations, derived from autologous fat and bone marrow with the majority targeting orthopaedic conditions including osteoarthritis (OA) and chondral lesions.[22,23]

In orthopaedics, the demand for cell therapies is driven by a lack of effective treatments for common conditions such as OA. Patients with OA of the knee in particular are inspired by the hope of a treatment that does not involve arthroplasty. This hope drives a willingness to pay for new treatments, even when not reimbursed by insurance providers.

While the progress of promising therapies should not be thwarted, clinicians and regulators have a duty to protect the public from the risks

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associated with unproven and uncharacterized therapies. When individuals place their hope and limited resources on ineffective forms of treatment, this can both waste their money and delay their access to more effective and appropriate treatments. Unfortunately, it has also recently been reported that patients have occasionally been harmed by uncharacterized treatments received at stem cell clinics. These include suffering significant bacterial infection,[24] paraplegia,[25] and bilateral loss of vision.[26]

While the overall rate of serious complications reported within the mainstream orthopaedic literature following cell therapies is low, the actual rate of complications of unproven cell therapies is unclear. Such data are often poorly reported from private clinics, where the prospective collection of data is less established than in academic units, and where financial pressures may have a greater influence on the reporting of poor outcomes or adverse events[27,28]. However, even simple procedures such as intra-articular injections of adipose-derived stem cells have some morbidity including pain and swelling, in up to 37% of patients, tendinitis or tenosynovitis in up to 22%, and rash.[29] Given the multipotent potential and immunosuppressive properties of certain cell therapies, concerns have also been raised regarding carcinogenicity.[30] While no cancer has been diagnosed, or has recurred to date in clinical trials involving experimentally given mesenchymal stem cells (MSCs),[31] there are laboratory reports of genetic instability and spontaneous transformation of MSCs into cells that are carcinogenic,[32,33] or support the proliferation of osteosarcoma cells.[34] While the risks remain low, it is clear that patients undergoing cell-based therapies require close monitoring until their safety in robust studies with long-term follow-up has been established.

Truth in advertising. Commercial providers of unproven cell therapies typically reach patients through online direct-to-consumer marketing. Analysis of advertising claims offers valuable insight into the techniques used by providers to promote their products. Often what is advertised is different from the actual treatment which is delivered. Several legal cases have highlighted a possible disconnection between advertising assertions regarding claimed 'stem cell' treatments and the cells which are actually administered.[35-37] These providers use a range of sales techniques to entice patients to pay for treatment, including exaggerating the benefits of treatment, using misleading or ambiguous nomenclature and strategies which are aimed at the perception of scientific legitimacy.[38]

Exaggerated messages. The data presented to support unproven cell therapies frequently overemphasize potential benefits while understating the risks, including the possibility of having no benefit. Clinics often describe 'growing new cartilage' or other tissues. To date, there is little or no evidence that available cell-based treatments for musculoskeletal conditions result in the increased formation of new tissue (i.e. have a 'structure modifying effect'). Clinics frequently make use of media accounts that sensationalize celebrity endorsements regarding efficacy, heightening public expectations. Misrepresentations of safety and efficacy build on exaggerated projections about the state of stem cell research, often in an extensive array of pay for publication journals that serve this market.[27,28] Few clinics collect data prospectively and report in a manner that would be acceptable for publication in established peer-reviewed journals.[39]

Table I. Summary of the criteria used to identify mesenchymal stem cells as proposed by the International Society for Cellular Therapies.[45]

ISCT criteria to identify MSCs
1. Culture-expanded cells
2. Adherence to plastic in standard culture conditions
3. Phenotype positive: (> 95%) CD105, CD73, CD90
4. Phenotype negative: (≤ 2%) CD45, CD34, CD14 or CD11b, CD79a or CD19 HLA-DR
5. In vitro differentiation: osteoblasts, adipocytes, chondroblasts (demonstrated by staining of in vitro cell culture)*In vitro* differentiation: osteoblasts, adipocytes, chondroblasts (demonstrated by staining of in vitro cell culture)

ISCT, International Society for Cellular Therapies; MSC, mesenchymal stem cell.

Misleading terminology. There is growing concern that uncharacterized, minimally manipulated cellular preparations from different sources are being misrepresented as stem cells.[40] The term 'stem cell' specifically refers to rare cell populations in native tissue that are usually resting, not dividing. They are induced to divide infrequently, but when they divide they do so in a manner that is 'asymmetrical'. This division results in 'self-renewal', with one cell returning to the resting state, and the other daughter cells expanding to generate cells, whose progeny can contribute to new tissue formation. Native tissue contains vastly more progenitor cells than stem cells and vastly more mature cells than progenitors. Under normal conditions, connective tissue progenitors (CTPs) are not detectable in human blood. In human bone marrow, a mean of one in 20,000 cells may be CTPs, with far fewer true upstream stem cells.[41,42] The bottom line is that while it is possible to refer to blood and bone marrow-derived therapies as 'cellular', if any true stem cells are transplanted they are one of the least common type of cell in the mixture. The use of the term 'stem cell therapy' is therefore an inappropriate and intentionally misleading misuse of the term that should be purged from advertising materials.[9,43,44]

The term 'mesenchymal stem cells' is also misused in marketing and research literature, contributing to confusion. MSCs, now mesenchymal stromal cells, are defined by the International Society for Cellular Therapy (ISCT) as culture-expanded plastic adherent cells that have trilineage potential and express defined surface markers (Table I).[45] Freshly isolated cells from tissue do not contain cells that meet these criteria. However, advertisements frequently lump together all the cells in native tissues that might contribute to either repair or immunomodulation under the banner of MSCs. This conflation between information known about the attributes and performance of culture-expanded MSCs and the highly heterogeneous and rare population of connective tissue stem and progenitors (CTPs) that are available in native tissues has resulted in considerable confusion among scientists, patients, clinicians and regulators.[46] Commercial bodies have seized on confusion in nomenclature to market unproven cell therapies for an inappropriate range of applications.[40] This feeds the misunderstanding on the part of patients and some providers that stem cells principally act to replace damaged and lost cells to restore normal function, despite limited clinical or preclinical evidence of long-term

Table II. Techniques used to build a case for credibility have been described as 'tokens of scientific legitimacy' (modified with permission from Sipp et al).[51]

Token	Explanation
Accreditations	Asserting certification of products or practices by international standards organizations
Boards and advisers	Convening scientific or medical advisory boards featuring prominent academics and business leaders
Trial registration	Registering trials to attract patients willing to pay to participate
Ethics review	Usage of the term 'ethics review' to convey legitimacy to products or procedures
Location	Renting laboratory or business space within a legitimate scientific or government institution
Membership	Joining established academic or professional societies to suggest legitimacy by association
Outcome registries	Publication of open-ended voluntary monitoring data sets rather than controlled clinical trials
Patenting	Suggesting that patent applications or grants indicate clinical use
Publication	Publishing research and commentary in journals with limited anonymous peer review
Rationales	Citing preclinical and other research findings to justify clinical application
Self-regulation	Forming organizations to self-regulate
Technical language	Using scientific-sounding words that suggest academic rigor
Endorsements	Providing expert opinions or celebrity comments on unsupported clinical uses

engraftment into musculoskeletal tissues, using cells from any source. It is becoming increasingly clear that the primary mechanism of action of transplanted cells is via a paracrine effect, by which the cells produce cytokines and other mediators that affect the local tissue environment, stimulating local, and perhaps distant host cells, to produce their biological effect.[47,48] However, much ongoing research attempts to establish methods of increasing engraftment efficacy.[49,50] These concepts are largely lost and poorly understood by those offering these therapies.

The perception of scientific legitimacy. In parallel to the conflated claims for biological therapies and the misuse of terminology, certain providers attempt to gain credibility by ascribing tokens of scientific legitimacy (Table II).[51] These include publications in journals with weak or non-existent peer review, renting laboratory or business space in credible scientific institutions and registering pay-to-participate 'clinical trials' on public databases. The use of such facsimiles of research activities as a persuasive indication of scientific credibility has become increasingly problematic.[52] Providers often register a study on a clinical trial database such as clinical trials.gov, and enrol patients who are paying for treatment in these trials, but fail to establish a formal system of retention and reporting. The result is the perception rather than the reality of research, and the outcome of many clinical trials that have been registered has never been reported. The guidelines of the International Society for Stem Cell Research (ISSCR) for Stem Cell Research and Clinical Translation strongly encourage the publication of both positive and negative results and adverse events, to ensure the development of clinically effective and competitive stem cell-based interventions and to prevent participants in future trials from being subjected to unnecessary risk.[53] Fung et al[54] assessed the extent by which registered clinical trials of innovative cell-based interventions report their results. In an analysis of publications from 1,052 novel stem cell clinical trials, 179 (45.4%) of 393 completed trials published results; 48 trials were registered by known stem cell tourism clinics, none of which reported results.

Marketing campaigns frequently overplay links with credible research and government institutions making unfounded claims about regulatory approval, scientific legitimacy and research evidence.[52] The potential for this type of advertising to reach a wide audience leads to concerns that the negative impact of these marketing campaigns may be greatly understated.[52] These techniques can be used to build a convincing case for legitimacy, and may distract or divert patients who are sincerely interested in contributing to a research effort from the opportunity for engagement with a true research centre. Due to these practices, without evidence that a given centre has been effective in publication and contribution to peer-reviewed literature, it can be difficult for professionals, let alone patients, to determine whether the claim of a research programme for developing and testing cell therapies is genuine.[51]

Recognizing the marketing of unproven cell therapies. The definition of unproven cell therapies can be confusing, but must be distinguished from the important process of identifying and defining promising new therapies that should be formally studied and documented as part of a formal research process designed to test safety and performance.[15] The core of this differentiation lies in the environment in which treatment is given which requires: a) a strong biological rationale; b) a balance of the information that is provided to patients; c) the presence of a defined protocol for patient selection and administration; d) commitment on the part of the patient and provider to the collection and reporting of outcomes; and e) the presence of appropriate independent oversight protecting the safety and rights of patients. While the legal definition of unproven cell therapies is the responsibility of the regulatory authorities of each state and country, several characterizations have been proposed to guide the cell therapy community (Table III).[15]

Challenges to the regulation of cell therapies. Any stem cell therapy should be approved by national or regional regulatory authorities, such as the European Medicines Agency (EMA), the US Food and Drug Administration (FDA), or Japan's Pharmaceuticals and Medical Devices Agency (PMDA). However, the regulations are different in different parts of the world. Some countries allow cell therapies that are prohibited elsewhere. In general, regulations in the USA and the European Union (EU) are considered more restrictive, while those in Japan and Australia are more permissive.[55] In the USA, cell therapies are regulated as biologics and are subject to premarket approval under the risk-based approach to approving cellular and tissue-based

Table III. Features of unproven cell therapies (modified with permission from Srivastava et al).[15]

Feature
1. Unclear scientific rationale to suggest potential efficacy
2. Lack of understanding of the mechanism of action or the biological function to support clinical use
3. Insufficient data from in vitro assays, animal models and clinical studies regarding the safety profile to support the use in patients
4. Lack of a standardized approach to confirm quality and ensure consistency in cell manufacturing
5. Inadequate information disclosed to patients to enable proper informed consent
6. Use within non-standardized or non-validated administration methods
7. Uncontrolled experimental procedures in humans

products.[56] Treatments considered 'minimally manipulated' are exceptions to this regulation, with the exact delineation of this term being the source of considerable controversy. In Europe, tissues or cells that are 'substantially manipulated' or targeting tissues different to their original source are subject to regulation through the EMA, with individual countries allowing exemptions. For instance, in Italy cells can be used in nonroutine cases on an individual basis. The Japanese government have invested considerably in stem cell science, generating new laws to expedite the path to clinical translation, and financially supporting scientific infrastructure. While the 'exemptions' to regulation in certain countries are often the most used routes by exploitative clinics, the lack of a harmonized regulatory also facilitates the evasion of regulatory oversight.[55] The establishment of global clinical trials and the work of international societies to educate government agencies are positive forces that may help to drive consistency in regulation internationally.

Striking a balance. Regulatory agencies are increasingly being challenged by calls for faster access to medical products, even in advance of the completion of rigorous clinical trials. Lobbyists and advocacy groups are promoting the deregulation of medical products and practices, including stem cell therapies.[55] This pressure may reduce the readiness of regulators and policy makers to oppose the commercial promotion of unproven interventions. The FDA is reviewing its regulations on human cell and tissue products, at a time when 'right-to-try' laws that aim to weaken federal oversight of investigational products to treat terminal illness have been passed in most states in the USA.[57] In addition, the 21st Century Cures Act includes mechanisms for accelerating approvals of legitimate cell therapies.[58] The recent acceptance by the FDA of OA as a serious condition further facilitates the advancement of cell therapies to treat orthopaedic conditions.[59] This ebb towards deregulation appears to be a global pattern. Conditional approvals that move the emphasis of efficacy testing to a postmarket setting have been introduced in Japan.[60]

However, there is no agreement that reduced regulation will be better for patients. Accelerated approvals limit premarket testing, thus imposing greater risks to patients. Direct marketing to consumers is more prominent in minimally regulated markets and patients in these settings must often make decisions about treatment without access to reliable information.[60] Providers are less accountable for claims made about efficacy, and it is therefore more difficult for physicians and patients to identify reputable sources of information about competing claims. This severely limits the ability of patients to make informed decisions and eliminates any incentive for investment in the development of definitive clinical evidence. It can thus be argued that deregulation increases the likelihood of the wasteful allocation of limited health care resources.

A call to action; encouraging good clinical practice. There are now broad professional recommendations to guide physicians offering new regenerative therapies. The ISSCR have published guidelines for research and the clinical translation of cell therapies.[61] In the USA, the Federation of State Medical Boards (FSMB) issued a report in 2018 entitled 'Regenerative and Stem Cell Therapy Practices' aiming to promote good clinical practice and the appropriate regulation of stem cell clinics.[62] These documents emphasize transparency, informed consent, consensual decision-making and the education of all stakeholders about what is currently known and not known about therapies. It is widely agreed among experts that new regenerative therapies should only be offered to a small number of patients outside formal clinical trials.[55] The FSMB report recommends that physicians should only offer treatments to patients for whom they have a bona-fide physician-patient relationship and that they must be appropriately trained to perform any proposed procedure safely and competently. Where evidence is unavailable for a treatment, physicians must only proceed when there is appropriate rationale and justification for its use, and only when accepted proven forms of treatment have been exhausted. As should be the case with all treatments, physicians should be entirely transparent in their education of patients about stem cell interventions and should alert them to reputable sources of information. Networks such as EuroStemCell (www.eurostemcell.org; largely funded by the EU) provide independent, expert-reviewed information and educational resources about stem cells and their impact on society. Several academic societies have invested considerably in public engagement and education resources including the ISSCR, who have an online forum for the education of patients (www.closerlookatstemcells.org). There is a desperate need for online resources that specifically address the use of cell therapies to treat musculoskeletal conditions.

Physicians must be able to support claims about the benefits of treatments with documented evidence. Given that cell therapy for orthopaedic applications is currently in a 'research phase', physicians should follow-up all patients, keeping an up-to-date database of outcomes and evaluating the data at least annually. Fees for treatments should not be excessive and all proposed treatments must be considered necessary. Shared decision-making should include as a minimum: an explanation, discussion and comparison of treatment options; assessment of the patient's preferences and values; a collaborative decision made with the patient, and an evaluation of this decision. Shared decision-making may help mitigate the risk of patients being exploited and ensure that consent to treatment has been provided in an informed manner.[63] The incorporation of these professional guidelines into formal regulation may encourage improved standards of clinical care.

Standards and best practice regarding the use of cell therapy. Researchers, industry, and clinics could improve clarity in the

communication of cell therapies by using transparent descriptions and by accurately reporting critical characteristics relating to the attributes and preparation of cells. A major challenge in this field remains the heterogeneity of preparations. While standards exist for the classification of tissues, materials and drugs, there are currently few standards for the communication and reporting of the characteristics of cell therapy.[9] The ISCT committee on MSCs has proposed minimum criteria for defining the term MSC and providers should ensure that the term is only used if these criteria are met (Table I).[45] A standardized measurement of the concentration, prevalence and biological potential of the CTP derived from native tissues should be incorporated into future clinical studies enabling assessment of the impact of variations among patients and the practices of the harvesting and processing of tissue.[44,64] Through a Delphi Process, a group of 34 international experts agreed on a descriptive tool (DOSES) for describing cell therapies that aims to allow researchers, clinicians, funding bodies and commercial organisations to communicate critical aspects of a cell preparation in a standardized fashion and rapidly.[65] Unfortunately, clinical trials evaluating cell-based treatments that have been published to date have failed to include sufficient experimental detail or to describe even basic attributes of the formulations delivered, including the basic characterization of the cells, all of which critically influence outcome.[4,5,66,67,68] This precludes interpretation of the exact nature of the cells delivered, prevents comparison between studies and makes replication by others impossible. Minimum standards of reporting have been recently introduced in an attempt to facilitate accurate critical appraisal of emerging studies evaluating cellular therapies (Supplementary Table i).[69] Physicians should also seek to convey clearly the characteristics of the cells which are delivered.

Registries have shown that they can provide important information about clinical outcomes and comparative performance of implants in patients. The orthopaedic community has a variety of successful registry platforms that can be adapted for use in biologics. Well-designed registries to include biorepository linked registries can provide important clinical information about the use of current and new biologics and cell therapies to treat common musculoskeletal conditions.[70]

Reporting illegitimate stem cell clinics. It is in the common interest of physicians, patients, industry and regulators to guarantee that there are clear pathways to the clinical translation of cell therapies. However, when individuals become concerned about the ethical or professional standards of marketing or clinical practices of a stem cell clinic or any other provider, there should be pathways which allow this concern to be reported to national and state medical boards, regulators (e.g. FDA, EMA), trading standards organisations, and other agencies.

Licensing medical boards. Patients can raise concerns about the practices of physicians to the medical board of the country or state in which they are practising. Medical boards have a responsibility to provide information about the reporting procedures of adverse actions related to stem cell interventions.[62] These boards may be immediately able to suspend practicing rights and so complaints to medical boards are taken extremely seriously by physicians. Recommendations have been published to guide boards about the reporting of clinics and providers when investigating complaints made against physicians.[62] When undertaking such investigations, medical boards are encouraged to review professional marketing materials and claims, including the websites of any clinic or physicians and information publicly available on online blogs or social media. Clear channels of communication between boards and regulators should be established to ensure that all parties are aware of potential infringements so that ongoing monitoring of professional conduct is robust. Where warning letters have been sent to licensees by regulators, medical boards should consider investigating these individuals, who may also be engaged in unprofessional practices related to the provision of regenerative therapies. In addition to actively monitoring potentially illegitimate clinics and responding to reports, medical boards should be encouraged to educate licensees on the federal and state legislation and guidelines regarding regenerative therapies, keeping licensees abreast of the changes as they happen. This may include generating educational resources and guidance documents that are widely disseminated and easily accessible.

Central regulators. Other agencies which may act to protect the public from potential harm include central regulators such as the FDA and EMA and trading standards organisations. Despite market and social pressures to increase access to these treatments, several countries have emphasized their commitment to enforce current regulations. The FDA has already taken various administrative and judicial actions in a small number of cases, and recently announced further strengthening of the enforcement of regulations and oversight of clinics offering regenerative medicine.[71-73] However, resources are limited and the enforcement of regulations in musculoskeletal settings may be perceived as a lower priority to regulators than targeting applications for conditions with higher mortality or morbidity.

Trading and advertising standards organisations. Trading standards organisations such as the US Federal Trade Commission (FTC) and UK trading standards aim to protect consumers by stopping unfair, deceptive or fraudulent practices. Many players make questionable marketing claims about their 'stem cell' offerings that could be considered false advertising. These organisations have developed exceptional tools to anticipate – and respond to – changes in the marketplace. While the FTC has now acted against two stem cell clinics relating to advertising standards, more must be done to harness this expertise and technology to identify rogue clinics.[74] Clinics offering suspicious therapies that may not be approved by national regulatory agencies, or that breach advertising standards can and should be reported to the authorities listed in Supplementary Table ii.

In conclusion, regenerative medicine is one of the most dynamic fields of science and medicine. While cell-mediated tissue formation and repair characterize all of biology, the prospect of specific augmentation of cellular processes through harvest, processing and transplantation remain in their early stages of development.[75] There are some unscrupulous providers and clinics that exploit the current hype surrounding cell therapies by making false representation and assurances to patients, and in some cases, expose patients to danger. This puts the entire field at risk, making products that are being thoughtfully and rigorously developed harder to advance. The challenge facing regulators is to balance increasing calls for faster access to

medical products, while protecting the public from unnecessary risks including delayed effective treatment, adverse events and financial loss. As a community of clinicians, researchers and patients we must strive for a culture of openness regarding the status of research and development, which balances benefits and potential risks of any new treatment. Similarly, we have a duty to protect current and future patients, should we become aware of clinics or providers who make false claims or expose patients to unnecessary risks.

Take home message

There is growing concern about the increasing number of clinical centres marketing stem cell therapies directly to patients

Inappropriate use of cell therapies threatens to thwart legitimate research effort and clinical translation

Regulators and clinicians must partner to develop recommendations for best practice

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