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EXPERT OPINION

Regulating the therapeutic translation of regenerative medicine

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Regenerative medicine and stem cell research are exciting new fields. But as the fields progress toward clinical therapies, controversies emerge. Hype surrounding stem cell research has caused an increase in their use in interventions that are not clinically proven. Furthermore, the regulatory agencies have a lot of difficulty dealing with cell therapies, which are distinctly different from drugs and medical devices they more commonly approve. To move the field forward, advocates, regulators and scientists need to come together to find new options for stem cell research oversight that protects both the patients and the research field.

Keywords: public policy, regenerative medicine, regulation, stem cell tourism, stem cells

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1. Introduction

Regenerative medicine holds the promise of restoring function to previously damaged tissues and organs by stimulating the body's innate repair mechanisms. Stem cells (SCs) potentially play a significant role in this process due to their capacity to differentiate into numerous cell types. Researchers are currently investigating the use of SCs in the treatment of many diseases, such as Parkinson's disease and acute macular degeneration, which currently have no cure and limited treatment options [1,2]. Embryonic SCs (ESCs) and induced pluripotent SCs (iPSCs) are attractive due to their ability to differentiate into almost all cell types. While there are several clinical trials underway for diseases such as age-related macular degeneration, there are not currently any treatments utilizing these cells that have been approved by the US FDA. In addition, there was a great deal of hope centered on a trial for spinal cord injuries utilizing glial cells derived from ESCs by the Geron Corporation, but this trial was halted in 2011 for economic reasons despite showing promising preliminary safety data [3]. Though ESCs and iPSCs have tremendous potential, the hype surrounding them has not been fully realized, and effective treatments may still be several years away. Unlike ESCs and iPSCs, adult SCs are more limited in their differentiation capacity. However, they have a proven track record of success, as adult hematopoietic SCs have been used for over 50 years in the treatment of blood diseases and cancers [2].

Clinics across the world have capitalized on the lure of ESCs and iPSCs and their use in regenerative therapies to market *adult* 'stem cell' injections as a cure-all for numerous diseases. SC tourism is a growing industry fueled by for-profit SC clinics that prey on the hope of patients desperate for a cure. As many of these clinics are undocumented, it is difficult to precisely quantify the number of patients who receive these therapies [1]. However, evidence suggests that the number of patients and clinics around the world are growing each year.

Ethical and political concerns underlie the operation of these clinics and can include unknown safety of procedures, trivialization of the potential risks, steep costs and limited regulatory oversight [2]. Herein, we argue for policy changes at

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the FDA and other regulatory agencies regarding these types of cell therapies. Regulation should streamline the clinical trials process and help potentially beneficial therapies get approved swiftly while also protecting the safety and rights of patients from fraudulent claims.

2. Stem cell tourism

Many SC clinics typically offer simple procedures and advertise unproven interventions for a host of diseases, many of which are terminal or degenerative where patients have access to limited therapeutic options. Though many procedures are proprietary and some offer ESCs or donated SCs, the majority are from autologous SC transplants. The patient first has SCs isolated, usually from his or her own adipose tissue, and later these cells are injected back into the patient at the site of injury or systemically. Many former patients claim that SC transplantation has helped them unequivocally as evidenced by numerous personal testimonies on clinic websites. More recently, many famous U.S. athletes have become spokespersons for these clinics and publicly claim that the procedures sped their recoveries [4]. However, these therapies have not undergone rigorous clinical trials for safety and efficacy.

Clinics market therapies by showcasing their apparent success with these prominent figures, a strategy that diminishes concerns surrounding the safety and efficacy of procedures despite the lack of empirical evidence [4]. Patients may view the fact that professional athletes have received the treatment as a sign that the procedures are both safe and effective [4]. Ultimately, these procedures can be very costly to patients, costing as much as $40,000, and are often not covered by health insurance policies, with clinics reaping the huge financial gains [5]. Regenberg *et al*. found that many clinics also suggest 'booster' doses of SCs, as some therapeutic benefits wane with time, leading to additional costly procedures [6].

Outside of financial risks, there are also health risks associated with these types of therapies. It is difficult to control the injected SCs' growth, and it is possible that this could lead to tumor formation. It is also unclear how SCs differentiate and where they reside after implantation. Furthermore, these cells are not typically monitored after injection. This could be problematic if undesired tissue began to grow or cells engrafted in the wrong site. There is also the emotional and psychological trauma of being promised a possible 'cure' for a chronic condition that ultimately may not be realized. More seriously, there have been several deaths worldwide attributed to unproven SC treatments [7,8]. These substantial risks are often not effectively and accurately communicated to patients, and the therapeutic benefit that patients will receive is often emphasized and exaggerated [6,9].

3. Regulation options for stem cell tourism

A major question moving forward is how to best regulate these interventions to deliver potentially beneficial treatments to patients while preventing costly and ineffective procedures. SC therapies should undergo greater scrutiny and clinical trials. Patient education and awareness of the potential risks of these therapies may not suffice because the decision to undergo treatment may not be solely based on scientific evidence, rather desperation [1].

Furthermore, some of the therapies currently fall outside of the FDA's purview. To fall outside regulation, the therapies have to meet certain criteria. First, the cells must only be 'minimally manipulated' [10]. This means that the cells' characteristics cannot be altered in any way such as treating them with drugs. The procedure must occur on the same day as the cell isolation. In addition, cells must be used for a homologous application: if tissue is isolated from a donor's bone, the cells must perform a basic function of bone in the recipient.

The FDA's guidelines, however, contain several ambiguities, and many scientists, physicians and ethicists support greater FDA involvement in overseeing these clinics. The definition of 'minimal manipulation' is vague, just as the interpretation of 'homologous application' is broad [10]. Ultimately, the clinics classify their procedures and use inexplicit FDA regulations to their advantage to deliver therapies lying within the gray area of regulation. Some of this suspect behavior was recently targeted by the FDA, which shut down SC therapies at several US clinics including Regenexx and Cell-Tex. These procedures involved injecting cells that had been isolated and subsequently grown in culture for weeks [4]. The FDA deemed that these cells were more than 'minimally manipulated,' functioning similar to drugs, and should thus be regulated as such. In part to target the types of abuses seen in these cases, the FDA updated the regulations in December 2014 and called for a public forum surrounding the proposed changes. These changes clarify and specify what is meant by terms such as 'minimal manipulation' or 'homologous use,' providing relevant scenarios and specific examples, particularly regarding adipose tissue.

There are several opponents to the FDA's decisions aside from the clinics. Many people feel that they and their doctors should be the final determiners of what is put into their body. Thus, patients may view the FDA as a threat to their sovereignty over their bodies rather than a facilitator that provides access to new and potentially effective therapies. As a result, several states have passed 'right to try' legislation allowing terminally ill patients to obtain therapies with the approval of a doctor and drug company. Critics argue that expanded access (or compassionate care) exceptions already allow for these types of therapies. Accordingly, the FDA grants ~ 99% of these requests to accelerate receipt of therapies prior to completion of the entire clinical trials process [11]. Furthermore, these critics foresee that these potentially unnecessary and unproven interventions could actually impair or endanger the quality of life of recipients. It is also critical to recognize that the owner must authorize the treatment or drug under right to try legislation, and these companies may be reluctant

to provide these potentially risky therapies [12]. Proponents of right to try legislation argue that expanded access has too many bureaucratic restrictions such as a tedious approval process in an already time-sensitive situation for dying patients.

Japan has responded to the issue of early access to therapies and drugs through two laws: 'The Act on the Safety of Regenerative Medicine' and the 'Pharmaceuticals, Medical Devices and Other Therapeutic Products Act' (PMD Act) [13]. Previously, clinical studies involving human SCs were performed under guidelines that were not legally binding. Under the new laws, any medical institution using SCs clinically must first submit their plan to a certified committee for regenerative medicine as well as the Ministry of Health, Labor, and Wellness (MHLW). Prior to these laws, the approval process for regenerative medicine technologies was similar to that in the US, requiring phased clinical trials to demonstrate safety and efficacy before the product was available on the market. The new laws grant conditional, time-limited marketing authorization of a product once it has been shown to be safe. Following this conditional approval, safety and efficacy must be confirmed continuously through post-marketing surveillance. If safety or efficacy criteria are not met, the conditional approval can be revoked. Otherwise, the product will receive a second marketing authorization [13]. Extensive informed consent documentation is required throughout. Furthermore, the legislation clarifies what regenerative medicine products entail and requires any cell-processing facility to obtain a license from the MHLW. Only time will tell if this experiment is successful at driving new therapies to the market or simply increases patient risk with treatments that are pushed to the clinic too soon and are not yet ready for mass distribution.

A similar push for accelerated access to drugs and therapies is gaining popular support in the U.K. The Medical Innovation Bill, also known as the 'Saatchi Bill,' permits doctors to attempt novel treatments on or administer new drugs to dying patients. Since the bill requires that these treatments first undergo peer review, it also relieves legal consequences of failed experimental therapies. The Saatchi Bill advances patient interests yet, like the PMD Act, challenges pre-existing conventions for determining safety and efficacy through the clinical trials process [14]. The U.K. Department of Health has endorsed the bill, and over 18,000 citizens have demonstrated their support for the legislation [14].

4. Policy changes and new regulations

Moving forward, relevant stakeholders, including patients, scientists, regulators and policymakers, should work together to provide guidance for and appropriate oversight of the clinical application of SC treatments. Although cell therapies cannot be judged and regulated in the same way drugs or medical devices are, they must be controlled somehow. The FDA should monitor existing clinics and procedures as well as the emergence of new clinics and work with them directly to establish clarified guidelines for permissible procedures. For example, the clinics should more adequately characterize the cells that are injected and do research to determine appropriate dose through a clinical trial process. Furthermore, clinics should demonstrate safety of the cells they are using. This data should be made widely available for investigative and public use. Only then, and through the regulatory process, should clinics be able to receive conditional approval to use SC injections.

In effect, the clinics should work together to assemble data of patients and initiate a form of clinical trials overseen and reviewed by a regulatory agency at minimum, although ideally they would complete the entire trial process. Patient outcomes should be documented, as is done in Japan, and any adverse effects should be reported immediately as recommended by ISSCR guidelines [15]. This would provide a mechanism to gather empirical evidence to determine efficacy. As a result, patients can be better informed of the details and potential benefits and risks of treatments they are receiving. Only with oversight by the FDA or similar regulatory authority should these patients continue to freely receive unproven SC therapies, and if treatments are ultimately determined to be ineffective, then the SC clinic should lose the right or ability to perform the procedure at all.

5. Conclusion

Regenerative therapies, particularly those that utilize SCs, will produce monumental advancements in the field of medicine. Yet SCs are still in the nascent stage of research, and many studies must still be conducted to determine their safety and efficacy prior to clinical translation. However, the FDA and other regulatory bodies must balance their role as regulator and facilitator of delivering new therapies to patients. A partnership between the clinics and the regulators would further benefit patients.

Declaration of interest

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