

The Global Emergence of Unregulated Stem Cell Treatments for Respiratory Diseases

Professional Societies Need to Act

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Despite the potential promise of new cell-based therapeutic approaches, unproven stem cell treatments for various ailments including lung diseases are a growing global problem (1). Notably, an increasing number of outfits offer expensive, cell-based therapies that are biologically implausible, known to be ineffective, or have no proven benefit. Falling under the umbrella term of stem cell medical tourism, these outfits prey on desperate patients with severe and often otherwise incurable diseases. In addition, there are documented cases of harm to recipients in some particularly egregious cases of unregulated use (2, 3). Remarkably, an increasing number of such clinics now operate within the United States. Hence, there is growing concern in the medical and regulatory communities (4, 5).

A number of international stem cell scientific societies and a growing number of professional medical societies have begun speaking out forcefully against stem cell medical tourism, and the U.S. Food and Drug Administration (FDA) has begun to take action against some of the outfits that offer unproven cell therapies (6–9). It is imperative that the professional respiratory disease and critical care communities take similar actions.

In the United States, the unproven therapy-based treatments that are currently offered to patients with respiratory diseases such as chronic obstructive pulmonary disease (COPD) and pulmonary fibrosis are mostly based on the extraction and

immediate (within hours) readministration of an autologous stromal vascular fraction (SVF), a heterogeneous mixture of immune cells, fibroblasts, endothelial cells, and stromal cells, or of mesenchymal stromal cells (MSCs) (10). As the FDA considers cultured MSCs more than “minimally manipulated,” and therefore subject to regulation as biological drug products (11), there are clinics that recruit patients with lung disease in the United States and perform the treatment with *in vitro* expanded MSCs abroad, often in Mexico or the Caribbean. Occasionally, extracted cells are combined with autologous platelet-rich plasma that purportedly potentiates their *in vivo* activity, although there is little evidence to support this approach. In both cases, the most common routes of cell administration are intravenous or intratracheal (in nebulized form). The treatments are purported to work through inflammation reduction or replacement of diseased lung tissue, or both, in timescales ranging from days to months. Most of the time, the claimed benefits are described in broad, qualitative terms such as “improved quality of life” and “increased energy/mood” instead of quantitative measures or outcomes. There are virtually no available data from appropriately designed and controlled clinical trials.

Unproven stem cell interventions for respiratory diseases are also available abroad, with India, China, Thailand, and Mexico hosting the majority of stem cell clinics. MSCs of various sources

(bone marrow, umbilical cord, and placenta) or hematopoietic cells from umbilical cord or peripheral blood are offered either as single or multiple infusion treatments. As with treatments offered in the United States, there are virtually no available data from appropriately designed and controlled clinical trials.

The increasing popularity of unproven stem cell interventions in nonclinical trial settings may seem paradoxical at first, especially in light of their unequivocal rejection by the vast majority of physician leaders and stem cell scientists. Nevertheless, perceptions of stem cell-based therapies can be significantly different between experts and the general public, including patients. Whereas experts evaluate therapies based on demonstrations of safety and efficacy, patients are motivated by hope and the desperate need for a cure (12, 13).

The wide divide in perceptions between vulnerable patients and practitioners of evidence-based medicine is exacerbated by several factors, including aggressive and unscrupulous direct-to-consumer advertisement of unproven stem cell-based therapies (14–16), uncritical and overly optimistic portrayal of stem cell clinical translation in mainstream media (17, 18), use of selected and uncontrolled patient testimonials to suggest benefit, and reluctance of experts to take an active stance against stem cell medical tourism because of fears of litigation and political backlash (19, 20).

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Moreover, lax, poorly defined, or nonexistent regulatory oversight in several countries has contributed to the proliferation of outfits offering untested and unproven stem cell treatments (21). Even in countries with efficient regulatory frameworks, such as the United States, clinics that offer unproven stem cell treatments for a variety of ailments have managed to operate by exploiting loopholes in current regulations (4, 22). Further, although some of these outfits are now registering treatment trials on ClinicalTrials.gov, this by itself is no guarantee for ethical conduct and does not confer or guarantee patient protection. On the contrary, the possibility exists that unproven stem cell- and cell-based therapy interventions that lack solid preclinical data may be advertised to the public and clinicians under the guise of registered phase 1 trials by abusing the mechanism of voluntary submission, and thus lending false credence to the unproven treatments (23).

To address this growing problem in the field of respiratory health care, the ATS Respiratory Cell and Molecular Biology

Assembly Stem Cell Working Group has intensified actions to counter stem cell medical tourism activities related to lung diseases. We posit that the problem of stem cell medical tourism of unproven, unregulated cell therapies can be best tackled through international collaboration and engagement and education of all involved parties including patients, physicians and other caregivers, and scientists. Judicious use of social media by respiratory societies, patient advocacy groups, and scientific organizations can engage patients and their families in a productive dialogue and provide them with a continuous stream of valid and up-to-date information on the dangers of stem cell medical tourism (24). Concurrently, information on properly vetted clinical trials and FDA-approved cell therapies can be disseminated.

In this spirit, a statement on unproven “stem cell” interventions for respiratory diseases has been posted online (25). This statement is supported by a growing number of international respiratory disease

societies and patient organizations. We anticipate that synergies between the participating organizations will soon lead to tangible results in terms of patient education about, and debunking of, unproven stem-cell based treatments for respiratory diseases. This effort also parallels similar efforts by respiratory disease foundations including the Pulmonary Fibrosis Foundation (26), Cystic Fibrosis Foundation (27), Pulmonary Hypertension Association (28), and Alpha-1 Foundation (29), among others, who have each recently issued notes of caution or statements regarding such treatments.

We can turn the tide on unscrupulous stem cell medical tourism only by vigorously implementing a multipronged strategy that combines continuous education of the public, pressure for effective regulations, and rigorous research in the field of lung regenerative medicine. ■

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