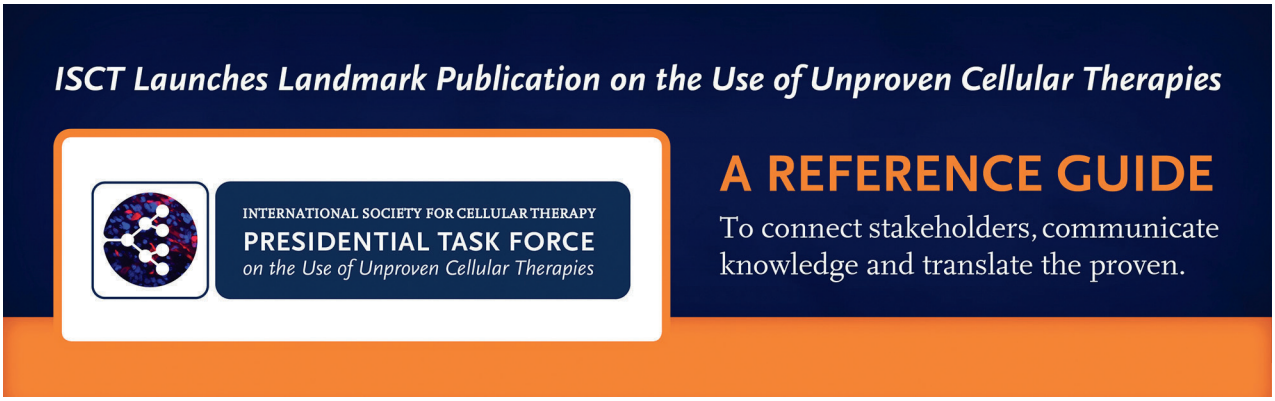

Cytotherapy, 2016; 18: 117–119

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Part 1: Defining unproven cellular therapies

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Introduction

Given the potential of cell-based products, including stem/progenitor cells and immune cells, there is a global effort to introduce these therapies into the clinic to correct organ dysfunctions, to treat cancer and to abrogate autoimmune diseases and a wide variety of pathological conditions [1–3]. Relatively easy access to these cells, obtained from marrow, adipose, cord blood and other human tissues, provides tremendous opportunity for translational research, particularly for indications with no satisfactory medical solution for patients with "unmet medical needs." Prenatal and adult stem cells (including induced pluripotent stem cells have significant potential to rebuild tissues and correct dysfunctional organs in human diseases. In parallel, certain populations of adult stem cells—notably mesenchymal stromal cells (MSC)—can also have modulatory actions in the absence of participating in structural tissue repair [4]. MSCs offer additional therapeutic benefits, of which the precise mechanisms of action are still under investigation. Similarly, the ability to isolate, modify and stimulate immune cells prompted their use within adoptive immunotherapy to treat cancer [5]. In the past two decades, technological advances have provided commercially available cell-manufacturing devices, reagents and delivery tools that enable processing, selection, expansion and storage of cells at a relatively low cost. Although these attributes form the basis for progressive acceleration in the field, they have also been associated with an increased early use of these therapies before being vetted

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(Received 28 October 2015; accepted 3 November 2015)

http://dx.doi.org/10.1016/j.jcyt.2015.11.004

within appropriate and adequate risk-benefit analyses. The use of cell-based interventions masquerading as "proven therapies" outside of approved clinical trials is a matter of even greater concern, as better understanding of several biological functions for many cell types in pre-clinical settings and in early controlled clinical trials is still needed.

Many of the cell types being investigated are readily accessible. Furthermore, there are fewer limitations related to intellectual property rights or cell-based technology methods than those customarily present during the development of small- and macro-molecule drugs. Although these freedoms promote robust, legitimate research and development, it has also led to the parallel development of clinics worldwide that offer cellular therapies with questionable safety or efficacy data or unclear scientific rationale for the treatment of a variety of diseases. This has led to vulnerable patients subjecting themselves to unproven cellular therapies in an environment with inadequate regulatory oversight or reliable information about potential risks or benefits [6,7].

How to define (and recognize) unproven cell therapies

The definition of unproven cell therapies is broad and could also be related to legitimate in-process research activities aimed to improve and verify certain cell-based approach hypotheses. Although new investigational medicinal products are tested under duly authorized clinical trials, many remain unproven or insufficiently proven. Unfortunately, many unproven or insufficiently proven cell therapies have been proposed to patients as "treatments or therapies" for a specific financial cost and without recognized biological and medical proofs of safety and efficacy (ie, without a positive benefit-risk assessment in place). Most of these therapies are offered outside of properly authorized channels and fall outside the realm of conventional clinical trial models, supervised and monitored by regulatory agencies (with the appropriate exceptions being compassionate use, or hospital exemptions). Although the legal definition of authorized cell therapy resides in the governing hands of each country's regulatory authority for drugs and therapeutic products, narrowing the scope to a handful of characterizations may assist the cell-therapy community to initiate the process of reaching a universal definition. The following series presents a starting point for clarification of defining an unproven cell therapy (Table I).

The lack of (reliable) information for patients on unproven cell therapies may be inversely proportional to the price for these treatments that are generally associated with a considerable economical and psychological impact for patients and their families. They generally take place in countries where such therapies are not regulated, and, for this reason, those practices have been dubbed "stem cell medical tourism" [8]. Recently, these practices have been occurring with greater frequency in countries where regulation is stricter but loopholes exist in the regulatory policies [9].

Table I. Characterization of unproven cell therapies.

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

Most of these unproven cell therapy scenarios provide very little local follow-up for treated patients. Since the clinicians involved are not required to provide data on their patients, few authentic reports of the success or failure of these therapies exist for appropriate peer review and regulatory oversight. Apart from being potentially unethical and possibly causing harm, unproven cell therapies may negatively affect the legitimate development of cell-based therapies.

Raising the interest on unproven cell therapies

Therefore, it is in the interest of the International Society for Cellular Therapy (ISCT; www.celltherapysociety.org) and other stakeholders within this field to raise awareness of unproven cell therapies. As a professional scientific organization, the ISCT maintains the power and authority to define how the world will develop cell therapy principles and processes. There is a particular need to determine what methods will be considered scientifically sound and ethically acceptable in this area of development.

The current environment is complicated to say the least. Varied circumstances exist throughout different parts of the world, thus creating diverse logistical, regulatory, social, economic and ethical challenges to developing this area of medicine. Furthermore, stem cells hold a nearly magical role in the eyes of patients. This leads clinicians to have an unusual amount of responsibility to properly communicate and moderate treatment expectations. To provide proper informed consent, patients must have a realistic understanding of cell therapy. How healthcare is

approached can differ by country. Adding to the complexity and intricacy of the situation includes an honest acknowledgment of the varying motivations among stakeholders within the field, from the idealistic scientist to the financially motivated capitalist, opinions color the landscape in shades of gray. Unfortunately, there are also individuals who use this opportunity to prey on vulnerable patients. As such, there is need to find common ground between all involved stakeholders to promote greater cooperation and a balanced approach that facilitates the development of safe and effective therapies and the patients' access to them without causing undue risks to patients or exploiting their vulnerability.

This text is an open, updatable document intended to be actively shared with other professionals (ie, bioethicists, scientific organizations and patient associations) as we work together to define and constructively discuss these issues and forge a path forward. With hastened immediacy, we also hope to promote a strategy for communication with patients considering unproven cell therapy as a treatment option. It is imperative that these people have the intellectual liberty to make an informed decision.

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