



PERSPECTIVE

Positioning a Scientific Community on Unproven Cellular Therapies: The 2015 International Society for Cellular Therapy Perspective

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Introduction

Currently, there are many unproven or insufficiently proven cell-based treatments commercially available for hopeful individuals seeking cures for a variety of conditions. Typically, these so-called “therapies” are currently being advertised, sold and administered to patients, although they fail to achieve recognized

biological/medical standards of proof for safety or efficacy. In addition, they are often expensive and offered outside the cover of routine clinical care for treatments, outside the realm of conventional clinical trials supervised and monitored by regulatory agencies. This paper summarizes a position document to be published by the International Society for Cellular Therapy (ISCT) as an open manuscript intended for

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professionals and patient associations. Avoiding a systematic overview of the relevant peer-reviewed literature and investigations, its purpose is to examine multiple aspects of unproven cell therapy interventions including definitions, manufacturing issues, regulations, economic factors and communication. With this document, the ISCT intends to promote a cooperative approach to facilitate the development of safe and effective therapies while minimizing and balancing risks for patients to ultimately establish a coalition of stakeholders that fulfill the vision of a broad, pro-patient cell therapy alliance.

The issue

The ISCT has identified key features of unproven cellular interventions and is now striving to promote effective communication strategies among individuals considering cell-based clinical interventions, patient associations and healthcare stakeholders [1]. These treatments have been occurring with greater frequency either in countries where regulatory policies do not address them specifically or in circumvention of existing laws [2,3]. Since the clinicians involved are not required to publish or otherwise share data, few credible peer-reviewed reports of the success or failure of these therapies exist. Furthermore, apart from being unethical and exposing patients to unnecessary risks, there is genuine concern that popularization of these unproven and possibly harmful cell-based interventions may negatively affect the legitimate development of evidence-based cellular therapies.

The need for proper conduct of cell-based therapy research

Cells are highly complex and change dynamically, both in response to their environment and over time. Thus, it is difficult to standardize cell-based treatments in the same way as drugs and molecular products that can be engineered and mass-produced. The practical utility of cellular therapies is also complicated by the fact that a positive clinical finding can be the outcome of one or more different mechanisms of action from the same intervention. By acknowledging these technical challenges in the establishment of safe and efficacious cellular therapies, within rigorously designed and carefully conducted clinical studies, it is possible to gather credible evidence concerning safety and usefulness of such products. Such evidence must be rigorous and independently verifiable. Evidence supporting claims concerning safety and efficacy must be generated before treatments can be distributed by professional cell therapy manufacturers, developers and suppliers of care practice [4].

Table I. Defining unproven cellular therapies.

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- Unclear scientific rationale to suggest potential efficacy
 - Lack of understanding of 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
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Definitions

With so many countries involved, the question resides in how to globally promote patient safety and address patients' interest in accessing unproven cell-based interventions. Therefore, it is important to define what we mean when we refer to "unproven cell therapies." The legal definition of authorized versus non-authorized cell therapy resides in the hands of each country's regulatory bodies. However, we hope to promote dialogue within the cellular therapy community by proposing a list of criteria that define unproven cell therapies (Table I).

The scientific principles and standards required to define and implement safe and effective "proven" cell therapies have been already largely shared [5]. This commences with a proof-of-concept testing based on *in vitro* research followed by appropriate pre-clinical animal models. Such "early-phase" evidence defines cells and mechanistic studies to possibly validate cellular mechanisms of action in a given disease [6]. Subsequently, well-designed and monitored clinical studies should be completed with cell-based products manufactured with the use of reproducible methods and under thoroughly controlled conditions. Clear documentation of prospectively defined, measurable clinical outcomes should establish safety and efficacy. Moreover, proper follow-up is necessary to determine long-term safety as an important component of conducting such research. Although the amount of data required to demonstrate efficacy depends on a variety of factors, peer-reviewed results and adequate regulatory pathways should assist in the approval of any therapy [7]. Depending on the disease, the regulatory environment and the type of cell-based intervention, this process can occur at the local, regional or international level and should be achieved by involving independent validation assessments.

Cell product manufacture and regulations

A detailed evaluation of the manufacturing facility and its operation is also important when assessing the

general safety and risk factors of a cellular-therapy product. Certification provided by a rigorous governmental agency or independent, internationally recognized accreditation body is the most reliable mechanism for evaluation. However, regulatory agencies and accrediting groups may not all provide equal degrees of assurance. Therefore, it is imperative to review credentials and potential conflicts of interests for these entities and ensure that they provide adequate oversight of manufacturing facilities and their operating processes. Cellular and tissue-based products are subject to complex regulations that vary widely according to country and product type. Consequently, from a regulatory perspective, how different products are categorized and regulated is context-dependent [8]. Many countries have used existing regulatory structures for conventional pharmaceuticals as a framework for regulating cellular and gene therapies. Other countries have developed new regulations for biologics or adapted regulations for drugs and medical devices to rule cell-based interventions. Therefore, it is important to assess how robust and rigorous the different national and regional regulatory frameworks are in identifying gaps and limitations in their design and enforcement. Inter-agency and international collaborations and even third-party accrediting organizations can assist in improving, enforcing and supplementing regulations. This process must be done while taking into consideration variations in socio-economic development, cultural norms, regulatory capacity and medical infrastructure.

Commercial practice

One of the most critical aspects of unauthorized unproven cellular therapies—commercial practices—directly affects the credibility and public acceptance of cell therapy approaches. Many contemporary cell-based interventions are advertised in a direct-to-consumer fashion without first being tested to determine levels of safety and efficacy [9]. Such premature commercialization represents a significant risk to both individual patients and healthcare systems. Claims made regarding unproven cell-based interventions vary widely, from the promising to the implausible. The unethical promotion of unproven cellular therapies is typically based on unfounded claims and is designed to appeal to vulnerable groups of patients. These dubious practices are exposing patients to unnecessary risks in individuals paying for stem cell interventions on the basis of hyperbolic, unsubstantiated claims.

Without actions by appropriate bodies, these unethical practices risk causing harm to patients and bringing the field of cell-based therapies into disrepute. A recent incident outlines once again that unproven cellular therapy includes the clear risk of

physical harm caused by poorly characterized products of unknown safety and efficacy [10]. Patients and their families are also exposed to financial risks and the possibility of dashed hopes and other forms of psychological harm. The risks of unproven cell-based interventions extend to healthcare systems as well. Direct-to-consumer marketing of unproven cell-based interventions can contribute to the undermining of regulatory frameworks intended to protect patients from physical harm and financial exploitation.

A global challenge

Globally, unproven cellular therapies require approval by regulatory agencies at different levels. In many countries, before applying for a biologics to patients, pre-clinical research and clinical studies are undertaken. In such regulatory environments, cell-based interventions must demonstrate safety and efficacy for a particular intended use in treatment of illnesses or injuries before entering the market. However, in some regions, there is pressure to move from regulatory frameworks requiring evidence of safety and efficacy toward a regulatory model in which only safety must be demonstrated before cell-based interventions can be marketed [11,12]. The implication of this less-demanding regulatory structure is that market forces will, over time, ensure that only the most efficacious interventions will be commercially successful. However, evidence of efficacy and therapeutic action of a defined cell-based product for specific clinical indication is highly relevant *a priori* in the solid establishment of a particular product into the clinic for patients to benefit and for its sustainability by healthcare systems.

Regional economic development strategies are beginning to include accelerated regulatory approval options, presumably as an enticement for investment [11]. On one side, this may represent a tightening of the standards for unproven cellular therapies in emerging markets; on the other, it may also reinforce a competitive regional landscape and bring therapeutic sponsors closer to non-traditional regulatory strategies.

Role of the ISCT

The ISCT and other related professional societies are well-positioned to promote a public dialogue to encourage the regulation of safe and efficacious cell interventions in all countries by recommending national and regional stakeholders to address and possibly remove scientific, technical and economic obstacles to clinical uses and commercialization of cellular therapeutics. Working together, a coalition of cell therapy societies could significantly affect public and private-sector perspectives in the cell-therapeutic space, thanks to increasing collaboration with regulators.

Table II. ISCT presidential task force on unproven cellular therapy proposals.

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- Establish a multi-lateral task force composed of patient organizations, professional societies and regulatory agencies to outline necessary actions to ensure patients are protected.
 - Implement a long-term program to promote global regulatory harmonization, including early access programs for unmet needs that permit cost recovery and reimbursement, and regulation that recognizes different tiers of risks and benefit and provides appropriate levels of regulation.
 - Establish a global, publically accessible, cell-therapy patient safety registry.
 - Promote rational scientific development of the field.
 - Enable ethical and compassionate early access to promising cellular therapies.
 - Cooperate with patient, scientific and professional organizations to leverage and share existing processes and resources with potential patients.
 - Provide tools to patients that can be used as guidance in evaluating a potential treatment.
 - Establish a reimbursement clearing house to assist early-stage companies that are developing ethical cellular therapies, an inexpensive source of reimbursement strategy and know how to implement the program.
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We are therefore recommending a series of actions to ensure that patient welfare remains of foremost concern in generating an increased level of public awareness of cellular therapy. The specific actions proposed for the coalition are detailed in Table II. A partnership between the various players in the field is needed. To enhance credibility and to minimize potential concerns about an industry-biased conflict of interest, it is also essential to include patients, patient organizations and patient advocates in the alliance. This alliance would need to balance the rights of patients to obtain treatment with their rights to participate in an ethical informed-consent process, in which all relevant risks and potential benefits are disclosed. Regulatory bodies would provide oversight, and review boards would ensure that yet-unproven interventions are tested in properly designed and ethically conducted clinical trials before commercialization occurs.

In conclusion, physicians, scientists, patient advocacy groups and professional societies play important roles in promoting informed decision-making by patients and helping patients understand the risks and benefits of any unproven cell therapy. While there is a long history of advances in biomedical research, there is an equally lengthy history of research abuses and profiteering from the sale of unproven and sometimes dangerous medical interventions. It is important to ensure that all research subjects are able to make informed choices, are exposed to a favorable risk/benefit ratio and are treated with dignity, honesty,

compassion and respect. The proposed coalition aims to help patients, research participants, researchers and respective associations to better assess unproven cell-based interventions in an informed manner and to promote understanding of key ethical, legal and scientific elements of human subject research.

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