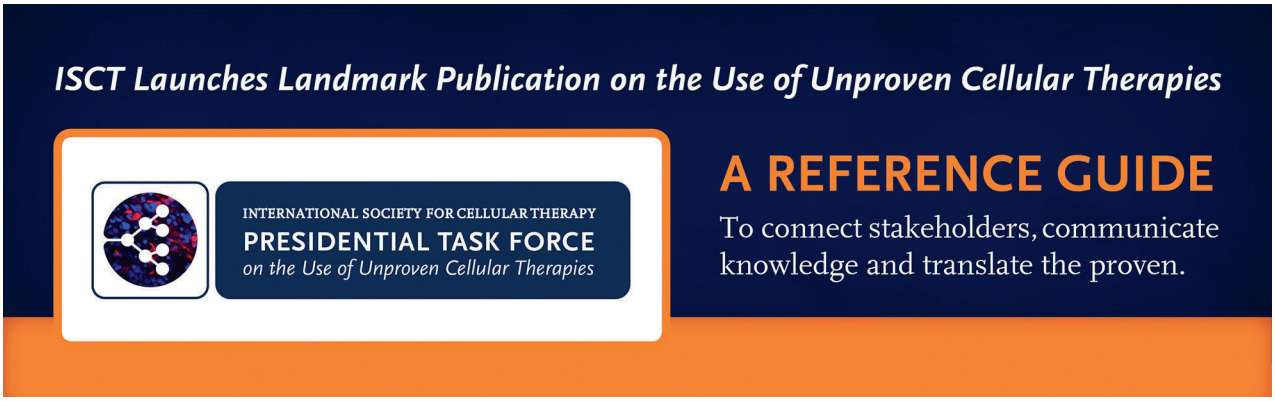


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# Part 5: Unproven cell therapies and the commercialization of cell-based products

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## The business of unproven cellular therapies

The market of "medical tourism" that broadly includes patients who travel for cheaper treatments because of the high cost of care in their own countries is approximately $20 to $60 billion and growing at constant rate [1,2]. We can estimate that the market for unproven cellular therapies can vary between $300 million and $2.4 billion on the basis of recent analyses reporting that more than 60,000 patients are treated every year with unproven cellular therapies [3], with an estimated charge for those procedures between $5,000 and $40,000 each [4]. Although these are significant numbers, in all likelihood most unproven cellular therapies will generate no predictable benefit for patients, despite the fact that in some countries the business of unproven cellular therapies is partly supported by governmental development strategies [5].

As previously described, there is a long and "inglorious" tradition of bogus medical treatment offerings for needy patients, predating the field of cellular therapy [6]. Unfortunately, presumed medical innovations, often prematurely described in the lay press as "treatments," quickly become the anticipated standard of care in the public eye and for patients who are often desperately looking for novel interventions. There are many factors limiting the diffusion and successful commercialization of cellular therapies; however, the ultimate success of the field is dependent on the level of regulation, in both the pre-marketing and in post-marketing phases of product development and translation. Without sufficient regulatory controls in place, unscrupulous commercial entities might be able to upset the commercial balance with unsubstantiated claims and unethical marketing practices. In addition, if patients are physically or economically harmed, there will be a detrimental effect further inhibiting the commercialization of cellular therapies.

In fact, if efficacy is never established and side effects are documented, then commercial

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entities will be hindered in their ability to generate a solid business case that could benefit industry, the biomedical field, society worldwide, and—most important—patients.

Furthermore, the market for unproven cellular therapies is volatile, particularly given that these therapies are often associated with countries with developing economies. A series of factors, including economic and political instability, policy changes, restrictions on travel, and advertising practices, contribute to such uncertainty [3].

Investors understand the difference between unproven cellular therapies and therapies that have been evaluated in a thorough development and regulatory process. They do not want to be associated with approaches that may be perceived as unethical, with uncertain risks and benefits, and that may be promoted in a misleading manner. Therefore, unproven cellular therapies, which are marketed as safe and effective, can have a destabilizing influence on financial sector confidence that emerging cell therapeutics are well founded and ready for development. These approaches, which lack an evidence-based development process, erode confidence that core therapeutic hypotheses have been validated. This further exacerbates concerns that scientific platforms are adequately durable to support clinical proof of concept, and therefore further restricts investment decisions in the cell therapy space. It is important for investors to understand the regulatory pathway for development of cellular therapies. For a typical investor, predictability and milestone achievements are critical to management of ongoing investments. The unethical commercialization of cellular therapies complicates the development pathway for an ethical developer and introduces an unpredictable factor into an investor's decision to invest in a cell therapy company.

For these reasons, it is difficult to identify big multinational players in the unproven cellular therapies field; more often, small to medium enterprises are involved with manufacturing sites located close to or in the same clinic where the patients are treated. Thus, cell manipulation and administration can take place within the same structure or institution, creating a sense of security about a product generated in house ("homemade") and, therefore, apparently more controlled. This goes back to the "black box of unproven cellular therapies manufacturing" and to the challenges for both established and under-development regulatory frameworks, as already discussed in Parts 3 and 4.

This "homemade" manufacturing model favors the gray area where unproven cellular therapies can proliferate with several advantages for the companies involved. A localized manufacturing process is less visible and less subject to regulatory and scientific scrutiny, a situation that typically characterizes these approaches. In addition, the entire process executed within a single clinic can provide the impression of a "compassionate use" that, without identifiable scientific bases and proper information, may be useless and even harmful. Finally, this model of unproven cellular therapies features a business model where cell manipulation takes place at relatively low production costs due to the limited controls introduced during the manufacturing process, and without investment into complex logistics or storage apparatus and procedures.

Advancing cell therapeutics to commercialization and standard of care requires significant capital investment from pharma and health care, and to date, although investments in the field are progressively increasing, they have been somewhat cautious. Investors are looking for predictability in a validated business model, an attribute that is currently growing in the field of cellular therapy but that is put in danger when discussing unproven cellular interventions. Industry players realize the importance of validation of key market segments, such as the ones for mesenchymal stromal cells or chimeric antigen receptor T cells. These are healthy signs reflecting a maturation that cannot be hindered by unethical, unproven, only-for-profit–based cell therapeutic procedures.

## Unproven cellular therapies, medical innovation and commercialization

One of the most frequent claims supporting unproven cellular therapies is that those strategies carry the unique opportunity to rapidly transfer promising cell-based therapeutic approaches for still-unmet clinical needs. This not only represents a marketing strategy "to sell" these products, it is also aimed at convincing society and patients of the innovative nature of the unproven cell therapy and to support the false concept that medical innovation is slowed, or even stopped, by consolidated regulatory frameworks. However, we contend that many unproven cell therapies are actually anti-innovative. We are naturally supportive of scientific and medical innovations in cellular therapies; however, we do not consider unproven cellular therapies as a solution for still unanswered medical questions. The last International Society for Cellular Therapy (ISCT) paper on the topic ([7], p. 966) stated: "Medical innovation in cellular therapy may be viewed as ethical and legitimate use of non-approved cell therapy by qualified healthcare professionals in their practice of medicine. Patients not eligible for controlled clinical trials should be able to choose unproven but scientifically validated cell therapy medical innovations, if the researchers are competent and those seeking treatment are truthful-

ly and ethically informed. There is a place for both paradigms in the cell therapy global community."

Traditionally, innovation in biomedicine has mostly been linked with academia and translated to industry. In that process, by pre-clinical experimental approaches, scientists and industry used intuition, observation and accurate data collection to draw results that were then further challenged in a relatively small number of patients. Those human subjects should be considered extremely precious for both ethical and business reasons; therefore, they should be carefully followed during and after the experimental treatments.

On the contrary, unproven cellular therapy strategies are generally introduced for a larger number of individuals with the stated intent of rapidly transferring the laboratory promise to patients without unacceptable waiting time. In this context, the loose scientific background together with the lack of basic scientific method [8] cannot be considered as a spark for innovation. In fact, after unproven cellular treatments, patients are generally discharged from the clinic with no or limited follow-up on either possible benefits or side effects. In this way, even if there might be some positive impact of the procedures, there is an absolute lack of interest in rigorously observing these outcomes to generate larger, controlled studies that are essential in validating hypotheses generated within clinical trials.

This abrogation of a scientific approach is generally unclear to patients, who are often given informed consents to read that can be misleading and result in the final decision to undertake risky procedures. Further details on this issue can be found in Part 6, which deals with communication.

## Counteracting distrust due to unproven cellular therapies

One of the most critical aspects of unproven cellular therapies—commercial practices—can be related to the negative impact generated by distrust of cell therapy approaches. This lack of trust is the consequence of lack of efficacy and from adverse events. The negative impact of aversion to innovation will be and has been felt by regulators, payers, prescribers, and, most important, in the court of public opinion. The unethical promoting of unproven cellular therapies is also of particular concern because it is based on unfounded claims and promises and targets vulnerable patients and families.

Regional economic development strategies are beginning to include accelerated regulatory approval options as an enticement for investment. This may represent tightening of standards for unproven cellular therapies in emerging markets but also reinforces a competitive regional landscape, bringing therapeutic sponsors closer to nontraditional regulatory strategies. There are, of course, provisions for accelerated or conditional regulatory approval for traditional pharmaceutical products. Heterogeneity in global regulatory approaches based on accelerated or conditional approval or, if different tiers of regulation are adopted in different regions, will inhibit true harmonized development of cell therapy products and ultimately retard development of the field.

The ISCT and related societies are positioned to work with regulators to implement harmonization of regulatory structures and to address commercialization roadblocks and can have significant impact on controlling public and private sector perspectives on the cell therapeutic space. Unfortunately, there has been little progress in this area to date, and for this reason, we are proposing a series of actions (Table I) to ensure that patient welfare is kept first and foremost in the agenda to increase trust regarding cells as therapeutic agents.

The goal is to extend ethical therapeutic sponsor and regulatory networks globally, such that incentives for operating outside the mainstream are

Table I. Proposed action steps.

1. Establish a multi-lateral task force comprising patient organizations, professional societies, and regulatory agencies to outline necessary actions to ensure patients are protected.
2. Implement a long-term program to promote global regulatory harmonization, including (i) early access programs for unmet needs that permit cost recovery and reimbursement and (ii) regulation that recognizes different tiers of risks and benefit and provides appropriate levels of regulation.
3. Establish a global, publically accessible cell therapy patient safety registry.
4. Promote rationale scientific development of the field.
5. Enable ethical and compassionate early access to promising cellular therapies.
6. Cooperate with patient, scientific, and professional organizations to leverage and share existing processes and resources with potential patients.
7. Provide tools to patients that can be used as guidance in evaluating a potential treatment.
8. 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.

reduced, and incentives for rational product development are in place. This can be achieved without diminishing economic development drivers or restricting cultural interests in clinical practice. If we work together to balance the rights of needy patients to receive unproven therapies with the protection of patients and we achieve a relatively harmonized global regulatory structure, this will benefit not only patients but also commercial organizations in the field.

## The economics of unproven cellular therapies

One important aspect of this issue is the practicing physician's views and behavior. The prescriber has a responsibility to educate and inform the patient. The physician or other primary health care provider should guide the choices of the patient when there are no available alternatives for the treatment of the patient's condition. The physician is there not to decide but to facilitate and inform decision making and should not shy away from expressing an opinion on the validity of some approaches when questioned by the patient.

If the physician or primary care provider prescribes unproven cellular therapies, this could generate support for those strategies and the perception that the approach could be acceptable or validated, despite the lack of what we normally would consider adequate evidence. This could also create issues in terms of reimbursement. In fact, a significant driver for unproven cellular therapies is the failure of patients to find promised new medicines reaching reimbursement expectations in traditional health care markets, driving individual patients to look for economic treatment solutions not accessible under traditional healthcare plans.

Patients are turning to unproven cellular therapies as an alternative when faced with a gap in approved therapies in standard of care and reimbursement policy. With approval in traditional markets in place, an economic driver in seeking nontraditional treatment remains. It is not unreasonable to anticipate medical treatments moving to regions providing reduced cost treatment—not unlike outsourcing manufacturing.

Patients certainly have the right to decide where to obtain treatment, provided they make informed decisions about the evidence supporting those treatments. There is also no issue when patients elect to travel to take part in bona fide and ethical clinical studies. The issue for patients is the manner in which unproven cellular therapies are sometimes marketed and promoted, with a minimum of efficacy or even safety data.

Thus, "medical tourism" is driven by an unmet market need, and while regions are moving to regulate activity, they are also acting to preserve market segment. Capital incentives to commercialize cell

therapeutics have become an important driver for regional economic development. Regulatory policy is becoming a tool to stimulate this regional economic development, with incentives for accelerating regulatory approval or providing access under unproven cellular therapies at the forefront. A key issue is when and whether private insurers are going to reimburse unproven procedures. The health technology assessments supporting reimbursement must rely on adequately generated and assessed medical evidence, even if sometimes limited, to constrain the use of unproven cellular therapies and further support provision of quality medical treatments.

## A call for a new global multilateral collaborative framework

Few professional societies have taken action on unproven cellular therapies. The International Society for Stem Cell Research has published patient guidelines for stem cell therapies [9], and ISCT has published a paper on the subject [7] and conducted several public workshops. In addition, the U.S. National Institutes of Health has published a web-based tool on stem cell therapies [10]. Unfortunately, the impact of these efforts has probably been minimal because most patients do not read the scientific journals or visit the society or government websites. In addition, there may be a perception that professional societies are excessively pro-industry and that their pleas for more regulation are based on anticompetitive interests rather than altruism and true patient concern.

Although bone marrow transplantation, as a paradigm for cell delivery in humans, has been used for almost 60 years now [11], the field of cellular therapy is still relatively young. Even so, a surprisingly large number of translational organizations have developed in the field, most of which have unique missions but also many overlapping interests. Unfortunately, there has been little cooperation among the cellular therapy organizations to date. What is needed is a broad alliance of the various players in the field. To enhance credibility and ensure that a patient's interests and rights are preserved, it is essential to include patients and patient organizations in this alliance. The alliance would need to balance the rights of patients to obtain treatment with the rights of patients to participate in an ethical informed consent process, where all relevant risks and potential benefits are disclosed. Without patient leadership, the alliance may be accused of bias toward large commercial players in the industry. It is our hope that, working together with a coalition of stakeholders, we can fulfill this vision of a broad, pro-patient alliance in the near future.

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