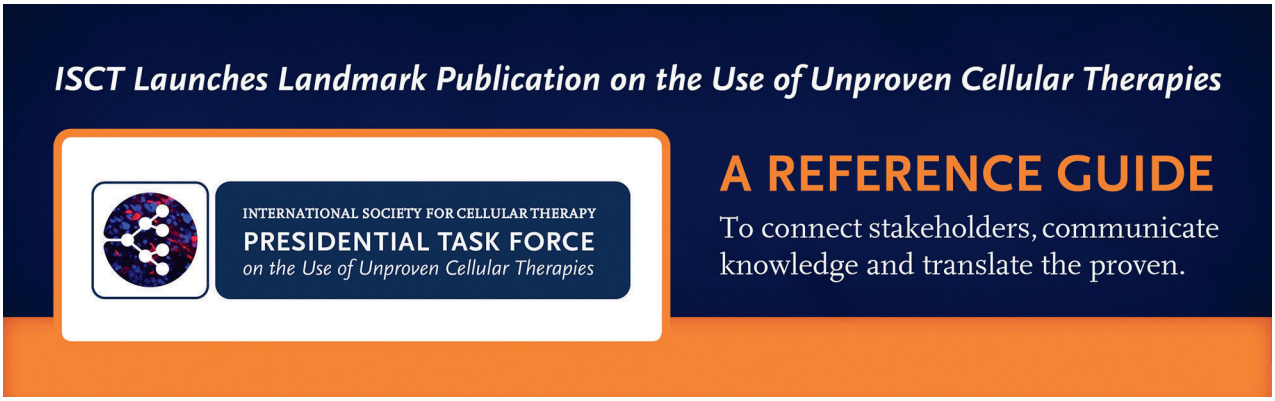

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Part 2: Making the "unproven" "proven"

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Introduction

The use of living, disaggregated cells in medicine involves a number of aspects that make this approach distinct from traditional pharmaceutical products. Cells are not metabolized by the liver or kidney, unlike most small-molecule drugs, but are potentially capable of distribution throughout the entire body. Cells are also highly complex and change dynamically in response to their environment and over time, making it difficult to standardize them in the same way that molecules can be engineered and mass-produced. Some type of cells may also secrete multiple bioactive molecules, such as cytokines and growth factors, as well as microvesicles, which may be released in different amounts or combinations, depending upon the cells' immediate environment or the pathophysiological state of the body into which they are introduced.

These properties of heterogeneity, complexity and malleability can make it challenging to test cell-based products through the use of paradigms developed for highly standardized and stable molecular products.

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This does not, however, mean that it is impossible to determine the safety and clinical usefulness of such products, nor does it remove the responsibility to provide rigorous, independently verifiable evidence from those who seek to develop cell-based interventions for commercialization or use in standard of care [1].

Therefore, the clinical translation of cell-based research toward development of specific therapies for a variety of diseases faces several challenges, not dissimilar to what took place in the 1990s during the early manufacturing of monoclonal antibodies for therapeutic uses [2]. After proper and rigorous assessments, these therapies are now used clinically for several diseases, with good success for large numbers of patients.

Next to (i) challenges related to the choice of a characterized cell type; (ii) understanding of its potential mechanisms of action for a specific disease; (iii) the technical aspects of its isolation, characterization and possible expansion under appropriate current Good Manufacturing Practice (cGMP) conditions; (iv) dose, dosing and mode of administration for any given clinical indication; and (v) the pre-clinical disease models in which to confirm proof of principle, it is crucial to define what evidence is needed to conclude that a particular therapy is safe and efficacious and can be considered as "standard of care," or at least a legitimate and viable option for that particular condition. Whereas the scientific aspects of this process can be reasonably defined, and should indeed be uniform worldwide, medical, regulatory, social and ethical aspects vary with respect to actual implementation of these approaches. These issues must be addressed to help the development of these therapies [3].

The scientific principles and the path required to move toward the goal of finding safe and effective cell therapies are reasonably well defined [4]. Initially, this involves developing proof-of-concept with both *in vitro* work and appropriate pre-clinical animal models, using clearly defined cells. Subsequent steps then include moving on to well-designed and monitored clinical studies with cells substantially or non-substantially manipulated through the use of reproducible methods under classified conditions. Clear documentation of defined and measureable outcomes that can establish unequivocal safety and efficacy must be included. Importantly, there should also be proper follow-up to provide proof of long-term safety. We also advocate that mechanistic studies be built into clinical investigations to provide further information to uncover and validate potential mechanisms of action of the cells introduced in a given disease [5].

One increasingly common approach is to offer autologous therapies in which cells are harvested from a patient's own bone marrow, adipose or other tissues and then are reinfused into the patient. Although this is perhaps less problematic in terms of safety issues, efficacy of such therapies must be evaluated by well-defined and measurable parameters. It is also important that long-term studies be performed for each potential clinical use. There is often little or no justification for claims of efficacy used to lure patients into undergoing these therapies. Furthermore, these approaches are most often done outside of legitimate clinical trials, without defined measurements of outcomes or adequate follow-up, and patients often pay large and unreasonable sums of money to undergo them [6].

"In case of emergency": compassionate use of cell therapies

At the same time, it is also recognized that in medical emergencies or other difficult medical situations that have exhausted other treatment options, the use of cell-based therapies may be implemented on a compassionate-use basis. Whereas regulations surrounding this vary in different countries, they must be applied in each situation with appropriate rigor. Furthermore, if a compassionate-use approach is found to be safe and consistently effective in any given disease, these instances should lead to the development of clinical trial protocols appropriate for that condition. Data from such trials will then be subjected to appropriate sharing and peer review.

The concept of "medical innovation" has been an important approach in the history of medicine for developing innovative therapies, but it still has to work within certain safeguards [3,7]. A system must exist within institutions that consider such approaches. This should rely on a physician presenting the need for such a therapy for a patient who has run out of options. An appropriate oversight committee then will be in place to assess this scientific rationale and the potential clinical benefit. This also must include a process to ensure that the patient or legal representatives have understood the unproven nature of such a therapy and to provide appropriate voluntary informed consent. It must also be ensured that the concerned physician or institutions have no conflicts of interest in promoting such therapies. Very importantly, no more than a few patients may be treated this way, after which a clinical trial protocol must be established if that particular approach must be continued.

If these principles can be followed universally, many of the current problems with unauthorized and illegitimate use of cell-based therapies may be avoided. However, the easy access to certain types of cells, frequently autologous mesenchymal stromal cells or immune cells, the unmet medical needs of desperate

patients and their families seeking care and potential for cure, as well as the business potential and financial gain from these interventions, have all led to a large and increasing number of centers around the world that offer cell therapies that are yet to be established as safe and effective to patients.

Needs and challenges of generating data on unproven cell therapies

The next important issue to address is the amount of data on clinical efficacy needed before a therapy may be considered to be of proven value for that condition. As with any other new potential therapeutic agent, this would require an initial well-designed and well-regulated phase (Phase 1) study assessing initial safety and feasibility studies that include attempts at defining appropriate doses to be used. These would then be followed by studies on efficacy and further safety studies (Phases 2 and 3), preferably in comparison to the best existing therapies, if any. Depending on the condition being treated, the selected end points, the sample size, and the trial design will vary, and the result would determine the status of that therapy.

In ideal circumstances, any new treatment would be considered to be not only effective but also the standard of care if it has been compared and found to be superior to the current best option in an adequately powered randomized trial. A parallel outcome would be that the new treatment is found to be not inferior to the current standard of care and thus be available as a legitimate alternative therapeutic approach. As mandated by the regulatory agencies in each country, there is no reason why these standards should not be uniformly applied worldwide for development of cell therapies.

We also acknowledge that in some ultra-rare, still-lethal conditions, large, sufficiently powered, Phase 3 randomized cell-based clinical trials, using reliable and valid primary end points, are not always feasible. For these situations, the scientific community, the healthcare providers and the regulatory agencies should allow early access to new therapies, including cell-based therapies. In such cases, a risk-based assessment should be taken into account that combines patient prognosis and safety aspects on manufacturing and delivery, with sufficient peer-reviewed scientific evidence of efficacy. A good example is the first gene therapy product that has been given market authorization by the European Medical Agency (EMA), an adeno-associated virus vector–based product for lipoprotein lipase deficiency [8].

Additional issues may arise from the way the cells are harvested and handled *ex vivo*, such as the case of the so-called, non-substantially manipulated autologous cells [9]. The debate on the topic continues as to whether these should be considered as medicinal products when utilized for non-homologous uses [10,11]. Regardless of autologous versus allogeneic use, or use of non-manipulated or manipulated cell products, it is imperative to generate rigorous peer-reviewed scientific evidence on their safety and efficacy and subsequent review by proper regulatory authorities before they can be used as medical treatment. Nevertheless, a regulatory agency (EMA) claims, "The Committee of Advanced Therapy classification is based on existing scientific knowledge of cell biology. Classification may vary according to the evolution of science." This suggests a framework for logical progression in which clinical development will follow and inform peer-reviewed science, and vice versa, in a mutually constructive relationship for the patient's benefit.

Challenges arise within these models at different levels and in different countries. If there is no system to support such a graded development process or if there is no access to the current standard of care in certain parts of the world, it will be difficult to apply the principles described above. Social and ethical issues with regard to access to some or any care may then come into the decision-making process for the approach to the development of these therapies in those countries. While making adjustments for those circumstances, it is critical to have independent review mechanisms of the process to ensure that the driving force is the concern for the patient and not any conflict of interest on the part of the physician or the institution. Going forward, the data acquired from such innovations must be peer reviewed, and a clear regulatory path should be devised for the further development and approval of these therapies [12]. Data should be reviewed by peers to decide when such a therapy may be considered to be adequately safe and effective as an option of treatment outside of clinical trials or indeed become the standard of care or a viable parallel approach. Depending on the disease and the type of cell therapy treatment, this could be done at the local or international level. As such, there is significant potential for cell-based therapeutic opportunities for a range of diseases, but only if investigated and validated in the most rigorous manner.

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