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# Medical Innovation Versus Stem Cell Tourism

Olle Lindvall<sup>1\*</sup> and Insoo Hyun<sup>2\*</sup>

Stem cell tourism is criticized on grounds of consumer fraud, blatant lack of scientific justification, and patient safety. However, the issues are complex because they invoke questions concerning the limits of acceptable medical innovation and medical travel. Here we discuss these issues and articulate conditions under which “unproven” therapies may be offered to patients outside of regular clinical trials.

Stem cell tourism is a worrying new form of medical travel driven by hope and pretense. Clinics around the world are offering unproven stem cell–based therapies to desperate patients for an array of intractable medical conditions. Such stem cell clinics have come under attack by scientists, clinicians, and bioethicists on grounds that they exploit seriously ill patients and threaten legitimate progress in the stem cell field (1). These concerns have found support in two recent publications. An analysis by Lau *et al.* (2) of online advertisements for stem cell therapies reveals that many clinics worldwide overpromise the benefits of their purported treatments and grossly downplay or ignore their attendant risks. And none backs up their claims with credible preclinical studies or other published scientific evidence. This is not simply another case of buyer beware; at stake is the potential for serious harm to vulnerable patients, many of whom may be too young to opt out of the proffered treatment. As a case in point, Amariglio *et al.* (3) report of a child who developed tumors in his brain and spinal cord after being treated with a series of poorly defined fetal stem cell transplants administered at a stem cell clinic. One might conclude from these examples that stem cell tourism—as the travel metaphor suggests—is teeming with medical tourist traps selling inauthentic representations of real medical treatment to unsuspecting consumers. The solution, many would argue, is for scientists to work with regulatory bodies to tighten regulations in offending locales and better educate patients.

These are sensible responses, but we must proceed carefully. The difficulty lies in being able to distinguish clearly between objectionable stem cell tourism and legitimate attempts at medically innovative stem cell–based interventions. This is crucial for two reasons: First,

failure to draw such a distinction makes it difficult to sanction against objectionable stem cell tourism and may hinder the development of ethically and scientifically responsible avenues for innovative stem cell–based care for patients with few or no acceptable alternatives. We must discourage objectionable stem cell tourism without eliminating the possibility of responsible medical innovation.

Second, the general issue of medical travel is complex, and demonizing all stem cell tourism runs the risk of giving short shrift to patients’ legitimate ethical motivations for such travel. Patients are not to blame, since medical travel may represent for them their last grasp at hope. Indeed, medical travel occurs in other areas of medicine, often involving highly innovative interventions at great cost to seriously ill patients, as happens today in cardiac centers of excellence all over the United States. Likewise, medical travel now and in the future may include “proven stem cell therapies,” i.e., stem cell–based treatments that have been established in the clinic and accepted by the scientific and clinical community. Such treatments, e.g., hematopoietic stem cell transplantation for leukemia, may not be available to patients in their own country. In due course, other proven treatments may be banned for political or religious reasons because of their use of human embryonic stem cells. Patients should remain free to travel to clinics offering established stem cell–based therapies. Thus, we must be able to distinguish between acceptable medical travel for innovative or proven therapies and problematic stem cell tourism.

The key question, therefore, is what are the hallmarks of an innovative stem cell–based medical intervention? To answer this question, we have to clarify the central difference between research, as carried out in a clinical trial process, and medical innovation. As explained in the seminal U.S. research ethics document, the Belmont Report, research aims at scientifically generalizable results (not patient care), whereas the goal of medical innovation is the benefit of the individual patient (4–6). Because of these disparate aims, the regulatory requirements for clinical research do not

serve as a proper surrogate for the ethical standards appropriate for attempts at medically innovative therapies (7). In short, the ethics of medical innovation is the ethics of patient care, not research. The research ethics paradigm views innovative treatment as a departure from standard treatment and overlooks clinical situations in which the currently accepted treatments are ineffective or burdensome (7).

From many patients’ point of view, consenting to medically innovative care may be preferable to enrolling in a clinical trial, especially where patient care is decidedly not the purpose of the trial—expanding knowledge is. Patients with precious little time might not care much about expanding knowledge; what they care about is getting better and surviving. Demonizing stem cell tourism will never squelch this vital instinct. Acceptable channels must be made available to seriously ill patients.

There are additional reasons why we must reserve space for stem cell–based medical innovations. One may not be able to rely solely on the clinical trials process—moving from Phase I, through Phase II, to Phase III trials to demonstrate safety, efficacy, and possible advantages compared to available treatments—to advance the field. We believe medically innovative care could be a powerful route, in combination with the clinical trials process, for developing proven therapies if conducted with rigorous oversight and scientific integrity. There exists an enormous array of possible stem cell–based interventions, depending, e.g., on cell type, homologous or nonhomologous use, site of delivery, autologous or allogeneic transplantation, and disease indication. The result of this plurality is that some stem cell–based interventions may be more akin to a drug intervention amenable to a multistage clinical trials approach, whereas others may align more along a surgical or transplantation paradigm, for which a clinical trials approach may be practically quite difficult to use, at least initially. In the last 40 years, only 10 to 20% of all surgical techniques were developed through a clinical trials process. Some specialties, such as cardiac transplant and laparoscopic surgery, developed entirely without clinical trials (8). Responsible medical innovation could be an important avenue for the development of stem cell–based therapies that follow a surgical paradigm or otherwise do not fit neatly into the square peg of the clinical trials process. Other approaches may evolve through the “off-label” use of approved stem cell–based interventions outside of a clinical trial, as has happened with many medical innovations in the past. In either of these cases, tough standards must be set forth to protect patients.

Developing a stem cell–based therapy via medical innovation alone is, however, not optimal. The clinical trials process enables one to compare the results of a procedure with the long-term outcome of alternative interventions, which is particularly relevant for stem cell–based therapies. These are in

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most cases meant to be replacement or regenerative therapies, for which long-term survival, lasting efficacy, and lack of serious side-effects are essential. The stem cell-based therapies must also be clinically competitive. Compared to available treatments, stem cell-based therapies have to offer more pronounced clinical improvement, fewer side effects, and/or lower costs.

Given the importance of both clinical trials and medical innovation, how should we proceed? The *Guidelines for the Clinical Translation of Stem Cells* (9), drafted by the International Society for Stem Cell Research (ISSCR), emphasize the clinical trials process in the absolute majority of translational stem cell studies (Fig. 1, left track). The principles include consistent starting materials, tests in animal models, review of protocols, and informed consent from patients.

Similarly, the ISSCR Guidelines offer standards for stem cell-based medical innovation. Currently, almost all stem cell-based approaches—aside from hematopoietic stem cell transplantation for blood disorders—are “unproven.” But there are important differences. The “magic cure by stem cells” approach (Fig. 1, right track), for which there is no scientific rationale or preclinical evidence of efficacy and safety, must be condemned in all circumstances. If there are no chances of improvement, the “therapy” is both unethical and scientifically and clinically unacceptable. Stem cell-based medical innovation (Fig. 1, middle track) encompasses approaches where there is a scientific rationale and for which efficacy without serious side effects has been demonstrated in animal models but the approach has not yet been established clinically. This may be due to poor availability of cells, limiting the number of patients who can be transplanted, or to

rapid scientific development with a need of further optimization before formal clinical trials should be started. This category should be acceptable outside formal clinical trials in few seriously ill patients who lack good therapeutic options. Although this proposal may seem radical to some, this is not a unique approach to medical advancement. As others have argued, efforts must often be made to advance a procedure to the point at which a formal research protocol can be developed (7, 10). These initial efforts may include clarifying the types of patients who might benefit from the proposed intervention and standardizing the procedures (7).

We emphasize, however, that stem cell-based medical innovations should be subject to a combined scientific and ethical review and proper patient protections (9). Again, this is not a new concept. In surgery, where medical innovation is both widespread and necessary for improving patient care, medical professional societies have previously wrestled with similar questions. As a result of this vital dialogue, The Society of University Surgeons recently issued ethical guidelines for surgical innovation (10). According to these guidelines, surgical innovators ought to submit a proposal to a local surgical innovations committee, which, like an ethical research board, would provide appropriate oversight, but within the context of patient care (10, 11). An analogous process for stem cell-based innovations has to be sensitive to the complexities of stem cell science. There should be a written plan that includes a scientific rationale, available evidence of efficacy and safety from preclinical studies in animal models as well as from applications of this intervention for other indications in humans, full characteristics of the

cells to be delivered, and description of mode of cell delivery and of clinical follow-up. This plan should be approved through a review process performed by experts, and there should then be a rigorous voluntary informed consent. Transparency of this review process and institutional accountability are also desirable and crucial for continued public support of the stem cell field. Following the experience with the medically innovative procedure, the physician-scientists should, whenever possible, initiate a clinical trials process. Due to the complexity of stem cell-based approaches and their strong foundation on basic research, medical innovations should only be applied by clinicians who are experts in the field and with close links to stem cell laboratories. Our recommendation here echoes the concept of “field strength” advanced by some writing in the liver transplantation field—namely, that the team performing the innovative procedure should have proven successes in relevantly similar procedures (12).

Given the current state of our knowledge about stem cells and their actions, patients should continue to be counseled against medical travel for unproven stem cell-based therapies at this time. In the near future, however, there will be a need to articulate further the acceptable conditions under which “unproven” stem cell therapies for specific diseases may be attempted, as medical innovation, in patients outside of clinical trials. In a world already flattened by the Internet and easy travel, this task will become increasingly difficult, especially as authoritative preclinical stem cell studies and legitimate clinical trials begin to offer promising results to the public. Thus, the public’s interest in stem cell tourism is likely to increase as stem cell science advances toward the clinic. There is much work ahead for the international community of researchers, clinicians, patient advocates, and regulators.

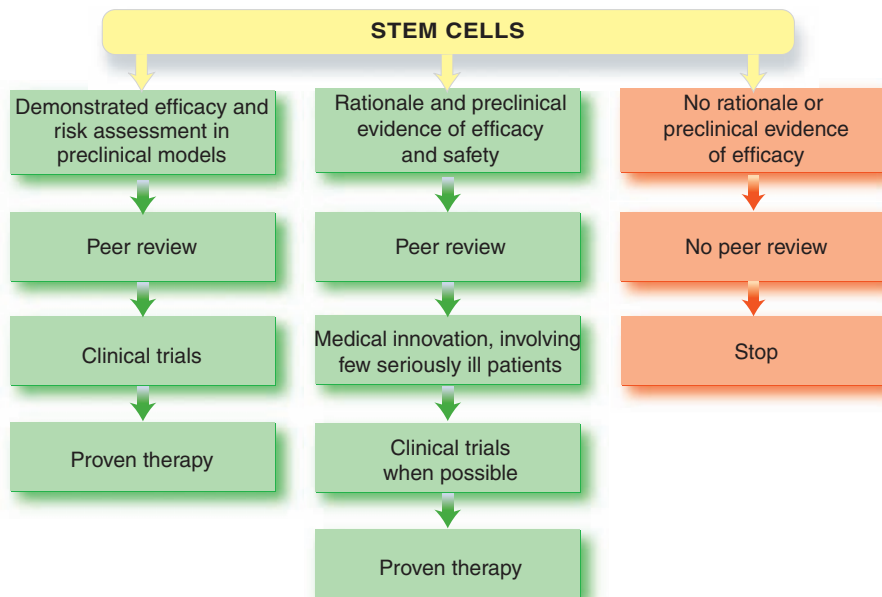


Fig. 1. Different steps in alternative processes for developing new stem cell-based therapies.

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