Cell Stem Cell
ISSCR: Committee Forum

Ethical and Policy Issues in the Clinical Translation of Stem Cells: Report of a Focus Session at the ISSCR Tenth Annual Meeting

Alongside the scientific barriers to the clinical translation of stem cell research are ethical and regulatory hurdles. Some of these challenges described by the Ethics and Public Policy Committee at the ISSCR Tenth Annual Meeting are presented here.

The clinical translation of stem cells will be associated with an array of scientific, ethical, and regulatory challenges, both expected and unexpected. While many of these issues were addressed in the International Society for Stem Cell Research (ISSCR)'s Guidelines for the Clinical Translation of Stem Cells (ISSCR, 2008), others have emerged over time. The ISSCR Ethics and Public Policy Committee organized a focus session at the 2012 Annual Meeting to raise and discuss some of the major issues to help ensure that the clinical translation of stem cells will be safe and appropriate (Table 1). The session addressed both preclinical barriers to translation (preclinical data; transfer and sharing of materials) and clinical barriers to human trials (trial design and comparators; perception and communication of risk to patients, families, and patient groups). Each of these topics was addressed by a concise structured talk, followed by short, invited commentaries. In this report, we provide a brief discussion of each topic and identify issues that warrant further discussion.

Preclinical Data

Successful translation of stem cell research into clinical applications must rely on a sound biological foundation, which includes high quality in vitro and in vivo preclinical data. The ISSCR's Guidelines for the Clinical Translation of Stem Cells describes the importance of preclinical studies in relevant animal models (ISSCR, 2008). While extensive in vivo preclinical work is conducted with rodents, Jason Robert queried whether rodent research is a sufficient foundation for the modeling of stem cell biology and human disease. Rodents are convenient and provide a tractable mammalian system for initial proof-of-principle in vivo and permit preliminary studies of safety and toxicity of prospective cell-based therapeutics. Moreover, because they are experimentally tractable, scientists have both the liberty and ability to perform research that is not possible in human beings. Yet using rodents exclusively or predominantly presents a host of conceptual, methodological, and ethical challenges for achieving translational success in stem cell biology. While work with them facilitates the research enterprise, it also fosters a certain abstraction from the historical, evolutionary, ecological, and developmental contingency of organisms in nonexperimental conditions (Robert, 2008). Further, this research runs the risk of blurring the lines between what we actually want to know and what we are capable of discovering. For example, while a rodent model might demonstrate success in the repair of spinal cord injury, whether such success would be expected in a human is unclear. Robert concluded with a call for research using a greater diversity of animal systems so as to justify more reliable inferences to humans, despite potential accompanying challenges such as those related to some types of experimentation with other nonhuman animals. Thus, there is a need for additional guidance on how these issues can be addressed in practice so as to help ensure safe and appropriate clinical translation.

Commentators described additional barriers to preclinical research, in particular those related to using human cells lines. These included limitations on the use of cell lines due to restrictions specified in the consent document for the collection of biological materials used to create the lines; questions about ownership of the lines (the scientist, the institution, or other entity); concerns about the appropriate oversight mechanism to employ (e.g., what constitutes human subjects research); and confidentiality of the genetic, medical, or other information associated with the cell lines.

Transfer and Sharing of Materials

Sharing of materials and data is crucial for the efficient progress of stem cell research and clinical translation. Several efforts have been directed at promoting the registration of, banking of, and access to stem cell lines and providing associated data, in particular for human embryonic stem cell (hESC) and induced pluripotent stem cell (iPSC) lines (Crook et al., 2010; Borstlap et al., 2010). An emphasis on clinical applications is increasing; for example, the Center for iPS Cell Research and Application (CiRA) at Kyoto University plans to establish a clinical grade, HLA-matched iPSC bank for clinical translation (Cyranoski, 2012). However, a number of barriers may hinder sharing, as outlined by Kazuto Kato and commentators. While sharing of materials promises to increase efficiency and the value of scientific endeavors, there is a lack of incentives in the system to encourage sharing, ranging from typical practices for publications to promotion and tenure, grants, and commercialization. Accordingly, thought should be given to developing appropriate incentives to overcome these barriers. In addition, securing funding for banks and databases is challenging because these activities do not generally make profits.

Other barriers include how to explain the use and transfer of cells and data at the time of informed consent, how to deal with the issue of communicating research results to donors, and how to protect the privacy of donors. In addition, the myriad of mechanisms to approve translational research remain confusing and burdensome, especially when the research is being conducted across cultural and international borders.

Table 1. Ethical and Policy Issues in the Clinical Translation of Stem Cells: Session Overview

	Speakers	Commentators
Introductory remarks	Jeremy Sugarman, Kazuto Kato	
Preclinical barriers: preclinical data	Jason Robert	Mahendra Rao, Shinji Miyake
Preclinical barriers: transfer and sharing of materials	Kazuto Kato	Kirstin Matthews
Clinical barriers: trial design and comparators	Jonathan Kimmelman	Peter Coffey
Clinical barriers: perception and communication of risk: patients, families, and patient groups	Douglas A. Sipp	
Group discussion		

Among these, the issue of privacy needs special attention, since stem cells such as iPSCs carry complete genomes of the donors. The stem cell field might look to human genome research, where systems have been developed for the protection of personal data while encouraging data sharing. For example, in an approach used by several large databases such as the database of Genotypes and Phenotypes (dbGaP) in the USA and the International Cancer Genome Consortium (ICGC), genomic data of individuals are shared with qualified researchers after strict review (controlled access) but data that do not lead to identification of individuals, such as aggregated somatic mutation data of cancer tissues, are freely available (Mailman et al., 2007; ICGC, 2010).

Trial Design and Comparators

Many therapeutic applications of stem-cell-based interventions involve surgical delivery. However, surgical procedures are associated with large placebo responses, observer bias, and effects on tissues that can mimic disease responses. Rigorous evaluation of stem cell interventions for safety and efficacy therefore requires randomized trials involving sham comparators. Jonathan Kimmelman suggested that such designs present at least two ethical challenges. First, they involve a relatively invasive form of belief manipulation, in which the investigator enacts a "theater of surgery." Second, they involve harm without direct benefit. Kimmelman argued that the ethical evaluation of sham comparator studies should begin by dividing sham risks into two components: the withholding of care (if any), and the performance of research procedures that have no compensatory direct benefit to the patient-subject. The former is justified provided conditions of clinical equipoise are met (Freedman, 1987). The latter becomes justified through a two-step process in which risk is minimized given the research objectives, and then the remaining risk is justified by an appeal to knowledge value. Looking forward, Kimmelman suggested that researchers should apply the following six practices when designing studies involving sham comparators: (1) use the term "sham" or "invasive placebo" rather than comparably benign language of "placebo"; (2) justify the selection of particular sham procedures; (3) justify the allocation ratio; (4) power studies adequately; (5) take additional measures to maintain blind, and test whether blind was maintained after the last endpoint; and (6) actively report sham-related adverse events.

Commentators highlighted the strong determination of those seeking experimental interventions. At a personal level, while the desire for access to new interventions for patients who do not have good available alternatives is completely understandable, there is great concern that using such interventions either prematurely because of the need for additional scientific development or outside of a controlled research setting may cause unnecessary harm. Further, while early human trials with those with end-stage disease is commonplace in oncology, it is still unclear whether this will be the right model for stem cell interventions because their biological properties as well as the comorbidities associated with end-stage disease may confound our understanding of safety and efficacy.

Perception and Communication of Risk: Patients, Families, and Patient Groups

The communication of risks in stem cell clinical research should be informed generally by the existing framework and practices established for human subject research in general but must also reflect the specific biological characteristics and behaviors of stem cells. Douglas Sipp pointed out that the properties that make various forms of stem cells potentially therapeutically valuable (such as proliferation, differentiation, migration/homing, and paracrine activity) could also make them harmful. For investigational protocols that propose to introduce stem cells or their derivatives such that they achieve lifelong functional integration into host tissue, the study design must reflect the potential consequences of studying a biological "drug" that is not expected to be metabolized or excreted by the body. This has profound implications for recruitment, informed consent, the ability of human subjects to completely withdraw from a study given that it may be impossible to remove the investigational product, and evaluation of safety, which may not become apparent for decades. Given the current atmosphere of hope, expectation, and optimism surrounding the therapeutic potential of stem cells, special care must also be taken to create realistic expectations of benefit, as patients may confuse stem cell clinical trials for treatments (Scott et al., 2010). Investigators need to exercise great caution in distinguishing stem cell clinical research intended to produce generalizable knowledge from treatment activities intended primarily for patient care.

Several audience members sought opinion about the ethicality, acceptability, and implications of clinical business models where human research subjects are asked or required to pay to participate in clinical research, such as whether, for example, this raises expectation of a positive medical outcome. This issue seemed to be especially important in lower income countries where research funding may be limited. Additional systematic information about this emerging practice needs to be gathered and then considered from legal, ethical, and scientific perspectives.

Discussion

Throughout the presentations and discussion, the tight relationship between science and ethics was clear, with ethical questions being coupled tightly to scientific questions. For example, the ethical and scientific issues of the use of animal models and their reliability and validity in predicting efficacy and safety work in tandem. Similarly, the selection of comparators in human trials raises questions about scientific objectives and validity. Addressing these issues together in the earliest possible stages of clinical translation promises to enhance not only the scientific and ethical quality of the research but also its efficiency. Moving forward will require identifying and describing models of how the scientific and ethical issues can be addressed concurrently during research design and oversight so that they can be disseminated and employed. The issues identified in this session provide a springboard for future scholarly work and policy development.

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