

New ISSCR Guidelines Underscore Major Principles for Responsible Translational Stem Cell Research

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The International Society for Stem Cell Research (ISSCR) task force that developed new *Guidelines for the Clinical Translation of Stem Cells* discusses core principles that should guide the responsible transition of basic stem cell research into appropriate clinical applications.

Rapid advances in all forms of stem cell research have raised the hopes of patients that they may one day receive new stem-cell-based therapies to relieve their disabilities or even cure them of their disease. While stem-cell-based therapies are the clinical standard of care for a few conditions, such as hematopoietic stem cell transplants for leukemia and epithelial-stem-cell-based treatments for burns and corneal disorders, the general public may not fully understand how many years of preclinical and clinical research will be required to bring novel stem-cell-based therapies to fruition. Unfortunately, there are some clinics around the world already exploiting patients' hopes by purporting to offer effective stem cell therapies for seriously ill patients, typically for large sums of money, but without credible scientific

rationale, transparency, oversight, or patient protections (Lau et al., 2008).

The ISSCR believes that administering unproven stem cell interventions outside a carefully regulated clinical trial puts individual patients at risk and also jeopardizes the legitimate progress of translational stem cell research. To address this concern, the ISSCR convened an international task force (Daley et al., 2008) to develop *Guidelines for the Clinical Translation of Stem Cells* (available at http://www.isscr.org/clinical_trans), which provides a framework for the responsible and timely development of clinically useful stem-cell-based therapies. Due to the wide variety of possible stem-cell-based treatments that may be pursued, the ISSCR guidelines offer a set of general

recommendations to researchers, clinicians, and those charged with overseeing research and clinical practice to assist their thinking about individual cases. The ISSCR guidelines pay special attention to issues that are stem cell specific while reiterating international standards of biomedical research, including independent peer review and oversight and strict adherence to high standards of voluntary informed consent. Below we summarize the fundamental professional and ethical principles underlying the recommendations set forth in the guidelines.

Major Principles

Independent Review and Oversight

Although biomedical research is already subject to peer review, regulation, and oversight, the ISSCR guidelines stress the importance of subject-specific expertise during review of translational research. Given the novelty and unpredictability of early stem-cell-based clinical trials, it is of utmost importance that individuals with stem-cell-specific expertise be involved in the scientific and ethical review at each step along the translational research process. Individuals with stem-cell-specific expertise are best able to assist investigators and human research review committees to assess the scientific underpinnings of the clinical trial protocol; the *in vitro* and *in vivo* preclinical studies that form the basis for proceeding to the clinical study; and the risks of abnormal product function, proliferation, and/or tumor development. The guidelines call on committees responsible for the oversight of human subjects research to draw on stem-cell-specific expertise in the evaluation of clinical protocols involving (1) products from human embryonic or other pluripotent stem cells; (2) novel applications of fetal or somatic (adult) stem cells; and (3) hematopoietic and other stem cells used for applications outside established standards of care. The ISSCR guidelines do not call for stem cell research oversight (SCRO) committees, established to review laboratory studies involving human embryonic stem cells, to conduct a separate review of clinical protocols, although some members of these bodies may be used as consultants to the review committees responsible for review and oversight of clinical research. In research locales without stem cell expertise, the ISSCR will help identify appropriate domain experts to assist in the human subjects review process.

The success of stem-cell-based therapies begins with the adoption of cell processing and manufacturing methods that promote maximal quality and safety of the cells to be used. The ISSCR guidelines emphasize the importance of accepted principles and practices of quality control conducted under expert and independent oversight at a level that is proportional to the degree of risk raised by the particular cell product and its intended use. The variety of cell types and sources, modes of processing, and biological variability creates significant challenges in the validation of cell products (Ährlund-Richter *et al.*, 2009). Systematic assessment of integrity and potency of cell products is essential to minimizing risk to patients. The task force recognized that the establishment of assays and surrogate markers will be refined over time and recommends that scientists and regulators work together to develop common reference standards, not only to ensure cell quality and safety, but also to facilitate comparisons across studies.

Preclinical studies are used to provide evidence of safety and to establish proof of principle for therapeutic effect. The ISSCR

guidelines underscore the importance of independent peer review in assessing preclinical data to ensure that clinical strategies are based on sound scientific rationale and adequate evidence for safety and efficacy before advancing to human clinical studies. Sufficient preclinical studies in relevant animal models are necessary to make proposed stem-cell-based clinical research ethical, unless approved, controlled, and conclusive human studies are already available with the same cell source and route of delivery. Rigorous preclinical testing in animal models—whenever possible for the clinical condition and the tissue physiology being studied—is especially important for stem-cell-based approaches because stem cells can act through multiple mechanisms, and because it is difficult to predict behavior in an animal from cell culture studies alone. Additional burden to demonstrate safety and efficacy falls on preclinical animal studies where cells have undergone extensive *ex vivo* manipulation and/or when the cells have been derived from pluripotent stem cells. Investigators may need to develop preclinical studies in both small and large animal models. The ISSCR guidelines acknowledge, however, the limitations of animal experiments in predicting how transplanted cells will behave in the human due to the context-dependent nature of cell behavior and the unique facets of human physiology. Thus, frequent interaction between preclinical and clinical investigators is strongly recommended to address unforeseen safety concerns, and a clear plan to assess the risks of tumorigenicity and any other adverse effects should be developed and reviewed prior to approval for clinical research.

Voluntary Informed Consent

As established in widely accepted international ethics documents pertaining to research with human subjects, voluntary informed consent is a cornerstone of ethical clinical research. The ISSCR guidelines recommend that special emphasis be placed on the unique risks of stem-cell-based clinical research during the informed consent process. These risks include sensitivities surrounding the source of cellular products, tumor formation, immunological reactions, unexpected behavior of the cells, and unknown long-term health effects. Research volunteers must be educated about the realistic potential for therapeutic benefit as they may have recourse to reasonable therapeutic alternatives and because they may harbor misconceptions about the potential for therapeutic efficacy. Moreover, the ISSCR guidelines recommend that research subjects' comprehension of relevant information—especially of the risks and uncertainties—be evaluated at the time of obtaining consent. For patients contemplating participation in stem-cell-based clinical research, the ISSCR provides information for patients in the appendices of the guidelines to assist their decision making.

Patient Monitoring and Adverse-Event Reporting

Risks to future research participants may be further minimized through careful patient-subject monitoring and timely adverse-event reporting. The ISSCR guidelines maintain that the welfare of research participants is of utmost importance and that their health must be carefully monitored throughout the duration of the stem-cell-based clinical trial. Given the unknowns of stem-cell-based clinical research, a data monitoring plan is required for all clinical studies, and aggregate updates should be provided to peer review committees on demand, based on adverse-event reporting and ongoing statistical analyses.

Furthermore, the ISSCR guidelines call on researchers to publish positive results, negative results, and adverse events and thus promote transparency, to prevent others from being subjected to unnecessary risk in future clinical research and to ensure the development of clinically effective and competitive stem-cell-based therapies.

Medical Innovation

Another key issue addressed is whether it is ever permissible for clinicians to attempt medically innovative care for their patients' benefit using stem-cell-derived cellular products outside the context of a formal clinical trial. The ISSCR guidelines acknowledge that there may be exceptional circumstances that allow clinicians to attempt medically innovative care in a very small number of seriously ill patients, subject to stringent oversight criteria. These criteria include independent peer review of the proposed innovative procedure and its scientific rationale, institutional accountability, rigorous informed consent and close patient monitoring, transparency, timely adverse-event reporting, and a commitment by clinician-scientists to move to a formal clinical trial in a timely manner after experience with at most a few patients. The task force believes that holding some current stem cell clinics to the standards outlined in the guidelines would identify significant shortcomings and call into question the legitimacy of their purported attempts at providing "innovative care" to their patients.

Social Justice and Other Aspirational Goals

The road to broad clinical translation of stem cells is likely to be long and fraught with challenges. As stem-cell-based clinical research activities are initiated and their numbers increase over time, it is imperative that principles of social justice be considered. A major justification for the public support of stem cell research is the promise of substantial social benefit, and therefore the benefits of research must be justly shared. The ISSCR guidelines recommend that translational stem cell investigators and regulatory bodies attend to issues of justice that are traditionally brought to bear in clinical research, including the fairness of subject selection and whether the participants will receive the benefits of research discoveries and therapies. Explicit attention paid to social justice, together with the other core principles articulated in the ISSCR guidelines, will go far in advancing the promise of stem cell research on both ethical and scientific grounds.

Looking Ahead

Around the world, new discoveries with clinical implications are continuously made in basic stem cell research, and stem-cell-based approaches are advancing rapidly toward application in patients. With these advancements comes the responsibility to attend to the safety and welfare of patients and research subjects at all times. The ISSCR is committed to ongoing review and revision of the *Guidelines for the Clinical Translation of Stem Cells* to keep pace with new developments in the field and to protect the interests of individuals and communities. The ISSCR guidelines should continue to promote the responsible translation of stem cell research into clinically competitive and effective, novel stem-cell-based therapies for various human diseases.

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