



ISSCR Statement on Delivery of Unproven Autologous Cell-based Interventions to Patients

September 11, 2013

- **The International Society for Stem Cell Research (ISSCR) urges medical licensing bodies, legal authorities, patient advocacy organizations, physicians, and others to exercise their influence to discourage commercial provision of unproven autologous cell-based interventions outside of clinical trials.**

Autologous cell-based interventions (ACBIs), which involve the collection and administration of a patient's own cells, have tremendous potential for treating a range of human afflictions. For specific cartilage, skin, and epithelial defects, and certain hematological and solid malignancies, specific treatments have been developed and shown to have therapeutic benefit, and the risks are well understood. For virtually all other diseases or conditions, researchers have not yet proven the clinical safety and effectiveness of ACBIs. However, such putative treatments are being offered to patients, often at significant expense, and on an increasingly widespread scale.

- *When professional consensus on the safety and therapeutic value of a treatment is lacking, the International Society of Stem Cell Research (ISSCR) believes it is unethical and unprofessional to market such interventions directly to patients.*

Discovering how to harness the therapeutic value of a new treatment strategy is arduous and time consuming. Unfortunately, the vast majority of potential new therapies that show promise in laboratories later prove unsafe and/or ineffective when tested in patients. This is true of new drugs and medical devices, and it is true of cell-based interventions.

Some of the risks and burdens associated with various ACBIs are well understood; these include risks of damage to tissues following administration of the cells, infection, and irreversible adverse outcomes caused by cells integrating into the wrong anatomical target. Some of the uncertainties that should be addressed prior to introducing a new therapy into widespread use in human beings include defining which particular cell preparations are useful for a given disease, how to prepare cells safely, what doses to administer, how to deliver cells to the right target, and knowing at what stage in a disease to use the cells. Risks associated with these factors are mitigated through extensive preclinical studies in the laboratory and through carefully designed trials in humans.

Despite known risks, the many uncertainties, and the absence of scientific evidence supporting efficacy, some clinics and companies are offering unproven ACBIs to patients for a wide range of diseases and injuries. Many of these "clinics" charge substantial fees to patients, and operate in jurisdictions that have little oversight of medical practice. However, even when clinics operate in settings that are subject to drug regulations and medical

licensing, there are often regulatory loopholes that limit the authority of regulators to control the use and marketing of ACBIs.

- *The ISSCR wishes to highlight the importance of proactive regulatory oversight for processing or manipulation of any medical product, including ACBIs.*

The provision of innovative therapeutic strategies to patients is essential to the advancement of medicine, and can be compatible with medical ethics. Unproven treatments that are believed by the medical and research communities to have clinical potential are most often given to patients in clinical trials so that their therapeutic value can be evaluated rigorously. In exceptional cases, unproven treatments are given to patients in the context of individualized care. However, the provision of unproven treatments to large populations of patients, particularly in a for-profit context, raises four major ethical and integrity concerns. First, by offering treatments that have known risks but unproven clinical value, it potentially violates the timeless ethical principle in medicine of “doing no harm.” Second, it potentially violates the patients’ autonomy by defrauding them- especially when ACBIs are portrayed as yielding therapeutic benefit before there is a scientific consensus. Third, if, as is often the case, provision of treatment does not allow for rigorous scientific assessment, it may impede the painstaking work of discovering how to unlock the true clinical value of a new strategy. Last, provision of unproven ACBIs on a large scale outside of a scientifically based clinical trial violates the high scientific and medical standards that have driven advances in stem cell medicine.

Indeed, there is precedent for harm from the premature introduction of ACBIs as routine care. Through the 1990s, many oncologists offered autologous bone marrow transplantation along with high dose chemotherapy as a treatment for metastatic and high risk breast cancer, based on preliminary evidence gathered from small, mostly uncontrolled clinical trials (1). A decade later, rigorous trials demonstrated that the approach was likely more toxic but no more effective than standard treatments for metastatic breast cancer. In the interim, tens of thousands of women were exposed to a harmful therapeutic strategy, at a cost of billions of dollars to the US healthcare system alone. In addition, widespread use of this unproven therapeutic approach outside of a trial made it difficult to implement the controlled trials needed to assess the clinical utility of the treatment.

In 2008, the ISSCR issued Guidelines for the Clinical Translation of Stem Cells (2) that offered recommendations for scientific, clinical, regulatory, ethical, and social issues that should be addressed before offering stem cells to patients. These guidelines were developed by a team of leading stem cell scientists, bioethicists, patient advocates, regulatory authorities, and physicians from 13 different countries.

- *The ISSCR Guidelines recommend that implementation of innovative stem cell therapies, including ACBIs, into broad clinical practice should only occur after scientifically sound preclinical studies and controlled clinical trials.*

The ISSCR guidelines support innovative applications of unproven ACBIs in patients outside the context of a formal clinical trial, only where the following conditions are satisfied:

- provision to at most a small number of patients
- a scientific rationale, including preclinical evidence of efficacy and safety
- full characterization of the types of cells being transplanted and their processing
- a peer-reviewed plan for the procedure and for clinical follow-up and data collection to assess the effectiveness and safety

- an action plan for adverse events
- a commitment to report results of innovative use
- moving to formal clinical trials in a timely manner after experience with at most a few patients
- *The ISSCR condemns the administration of unproven stem cells or their direct derivatives to a large series of patients outside of clinical trials, particularly when patients are charged for such services.*

These recommendations are consistent with numerous other national and international policies on innovative treatment and trials (3, 4). For instance, the World Medical Association's Declaration of Helsinki (5) states that where unproven interventions are given to patients, they "should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available." Unfortunately, many clinics that offer ACBIs do not meet the above conditions.

References

1. Rettig, R.A., Jacobson, D., Farquhar, C.M., and Aubry, W.M. (2007). *False Hope: Bone Marrow Transplantation for Breast Cancer* (New York, Oxford University Press).
2. International Society for Stem Cell Research (2008). *The Guidelines for the Clinical Translation of Stem Cells*.
http://www.isscr.org/clinical_trans/pdfs/ISSCRGLClinicalTrans.pdf. Accessed August 20, 2013.
3. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1979). *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*.
<http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html>. Accessed August 20, 2013.
4. American Academy of Pediatrics Committee on Drugs (2002). Uses of drugs not described in the package insert (off-label uses). *Pediatrics* 110, 181–183.
5. World Medical Association (2008). *Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects*.
<http://www.wma.net/en/30publications/10policies/b3/>. Accessed August 20, 2013.

The International Society for Stem Cell Research is an independent, nonprofit organization established to promote and foster the exchange and dissemination of information and ideas relating to stem cells, to encourage the general field of research involving stem cells and to promote professional and public education in all areas of stem cell research and applications.