5215 Old Orchard Rd, Suite 270
Skokie, IL 60077 USA
Tel: +1-224-592-5700
Fax: +1-224-365-0004
isscr@isscr.org
www.isscr.org

DATE: 5 July, 2016

TO: Committee on Human Gene Editing: Scientific, Medical, and Ethical Considerations
National Academy of Sciences and National Academy of Medicine
500 Fifth Street NW
Washington, DC 20001

FROM: International Society for Stem Cell Research

RE: Human Gene Editing: Scientific, Medical, and Ethical Considerations

The ISSCR is an independent, nonprofit membership organization established to promote 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 application. The ISSCR is the world's largest professional organization of stem cell scientists, with approximately 3700 members from more than 55 countries.

The ISSCR 2016 Guidelines on Stem Cell Research and Clinical Translation

On 12 May 2016, the ISSCR released newly updated Guidelines for Stem Cell Research and Clinical Translation, prepared by an ISSCR task force of 25 scientists, ethicists, and experts in health care policy from nine countries (Daley et al., 2016; ISSCR, 2016). In the development of these guidelines, the ISSCR task force recognized that rapidly evolving technologies like gene editing provide unprecedented opportunities to understand human biology and disease and to explore new approaches to medical treatments. They also raise questions that have legal, social, and ethical implications. Through its guidelines, the ISSCR promotes rigorous scientific inquiry, medical progress, and careful ethical deliberations. The guidelines provide confidence to practitioners and the public that stem cell science can proceed efficiently and remain responsive to public and patient interests.

The ISSCR developed earlier sets of guidelines that are widely followed by researchers and institutions around the world (Guidelines for the Conduct of Human Embryonic Stem Cell Research, 2006; Guidelines for the Clinical Translation of Stem Cells, 2008). These guidelines have been very influential, providing a basis for implementing new regulatory or oversight practices in countries without existing regulatory infrastructure as well as internationally applicable ethical standards for research required for publication by scientific journals. The 2016 guidelines update and expand the 2006 and 2008 documents and bring all guidance together under common principles of research integrity, patient welfare, respect for research subjects, transparency, and social justice. The 2016 guidelines continue to build on widely shared principles in science, calling for rigor, oversight, and transparency in all areas of practice. Key elements of the guidelines and a synopsis of their recommendations are presented in an article from the ISSCR task force (Daley et al., 2016).

The 2016 guidelines reiterate the ISSCR's position on germline nuclear genome editing. The ISSCR supports laboratory-based research that entails editing of the nuclear genomes of

human sperm, eggs, or embryos, when performed under rigorous review, but hold that any attempt to apply this clinically would be premature and should be prohibited at this time.

The 2016 guidelines preserve the imperative for a specialized oversight process for research involving human embryos, in recognition of the unique sensitivities surrounding such research. The 2016 guidelines specify a process of embryo research oversight (EMRO) which reviews both embryonic stem cell research and human embryo research that may not explicitly pertain to stem cells or stem cell lines, including genetic manipulation of human embryos or gametes used to make embryos *in vitro*. At present, the guidelines for EMRO review represent the most comprehensive set of principles to inform oversight of the emerging technologies being applied to human embryo research. The EMRO process would replace Embryonic Stem Cell Research Oversight committees and broaden their purview by incorporating oversight of human embryo research.

Germline genome editing

Genome editing, the purposeful modification of the DNA sequence in a cell, has played an essential role in biomedical research for several decades, allowing scientists to investigate disease and develop new medical treatments. After many years of foundational research on gene transfer into mammalian cells, numerous clinical trials are currently underway that employ genome editing approaches in somatic (non-reproductive) cells and represent promising strategies for correcting inherited immune deficiencies or treating cancer.

Technologies used to introduce changes into the DNA sequence of cells have advanced rapidly, making genome editing increasingly simple. For example, zinc finger nuclease-, TALEN- and CRISPR-Cas9- based technologies are being used by researchers around the world to introduce or correct mutations in targeted sequences in a wide range of cell types.

Genome editing is feasible, not just in the somatic cells of an adult organism, but also in early embryos, as well as the gametes that carry the inheritable, germline DNA. Research involving germline nuclear genome editing has been performed to date in many organisms, including mice and monkeys, and applications to human embryos are possible.

Any consideration of applying nuclear genome editing to the human germ line in clinical practice raises significant ethical, societal, and safety considerations. Current genome editing technologies carry risks of unintended genome damage, in addition to unknown consequences. These are of much greater concern in the context of the germ line, where, unlike changes in somatic cells, genetic changes alter the genetic makeup of every cell in the body and/or are passed down to future generations. Moreover, consensus is lacking on what, if any, therapeutic applications of germline genome modification might be permissible. For example, some argue that the ability to eradicate disease justifies attempts at therapeutic editing of the human germ line, while others emphasize the difficulty of drawing clear distinctions between applications in human disease and attempts at human enhancement.

In a statement published in April 2015, the ISSCR supported *in vitro* laboratory research, performed under proper ethical oversight, to enhance basic knowledge and to better understand the safety issues associated with human genome editing technologies, including their potential for application in somatic tissues. The ISSCR also called for broad public and international dialogue on the capabilities and limitations of these technologies and on the implications of applying them to the human germ line. The ISSCR applauds the National Academies for the role they are playing in this discussion.

In Section 2 of the 2016 “Guidelines for Stem Cell Research and Clinical Translation,” the ISSCR further articulated its position and called for rigorous oversight of research using human embryos (detailed in Section 2.1):

"Recommendation 2.1.4: The ISSCR supports laboratory-based research that entails modifying the nuclear genomes of gametes, zygotes and/or preimplantation human embryos, performed under a rigorous Embryo Research Oversight (EMRO) process. Such research will enhance fundamental knowledge and is essential to inform any thoughtful deliberations about the potential safety and use of nuclear genome modification in strategies aimed at preventing the transmission of genetic disorders. Until further clarity emerges on both scientific and ethical fronts, the ISSCR holds that any attempt to modify the nuclear genome of human embryos for the purpose of human reproduction is premature and should be prohibited at this time.

The guidelines go on to separately address mitochondrial replacement therapy, a form of germline modification that entails replacing the mitochondria, found outside the nucleus, in the eggs of women at risk of transmitting certain devastating diseases to their children:

"In contrast, mitochondrial replacement therapy employs distinct methods and does not entail direct modification to the nuclear genome. Preclinical research into the safety and efficacy of mitochondrial replacement strategies is now underway and should continue under appropriate regulatory oversight. Thoughtful scientific and ethical discussions of this technology have recently occurred in the U.K., the U.S., and elsewhere in the world (U.K. Department of Health, 2014; National Academies of Science, Engineering and Medicine, 2016). Guidance provided by these prior reports, as well as within these guidelines provide plausible mechanisms of review, approval, and oversight of clinical translation of mitochondrial replacement therapies."

Clinical application of genome editing approaches in somatic cells

The ISSCR's Guidelines for Stem Cell Research and Clinical Translation highlight scientific, regulatory, ethical, and social issues that should be addressed so that basic research is responsibly translated into appropriate clinical applications. A summary of the recommendations can be found in Daley et al., 2016, attached here. In brief, the guidelines highlight opportunities for researchers to strengthen preclinical studies, call for new stem cell treatments to be tested for safety and effectiveness in well-designed clinical trials, and emphasize the imperative of evaluating potential new treatments against local standard of care.

As in any area of technology where there is a widely held expectation of therapeutic promise, timely and balanced communication is very important. The ISSCR guidelines highlight the responsibility of all groups communicating stem cell science and medicine—scientists, clinicians, industry, science communicators, and media—to present accurate, balanced descriptions of progress and setbacks.

References

Daley, G. Q., Hyun, I., Apperley, J. F., Barker, R. A., Benvenisty, N., Bredenoord, A. L., Breuer, C. K., Caulfield, T., Cedars, M. I., Frey-Vasconcells. J., et al. (2016). Setting global standards for stem cell research and clinical translation: the ISSCR guidelines. Stem Cell Reports *6*, 787–797.

International Society for Stem Cell Research (ISSCR). (2015). ISSCR Statement on Human Germline Genome Modification. http://www.isscr.org/docs/default-source/guidelines/isscr-statement-on-human-germline-genome-modification.pdf

International Society for Stem Cell Research (ISSCR). (2016). Guidelines for Stem Cell Research and Clinical Translation. http://www.isscr.org/guidelines2016