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19 August 2021

Mr. Ong Ye Kung
Minister of Health
16 College Road
College of Medicine Building
Singapore 169854

Dear Minister Ong:

On behalf of the International Society for Stem Cell Research (ISSCR), I write to express our support for clinical research using mitochondrial replacement techniques (MRT) to prevent the transmission of serious mitochondrial diseases. The ISSCR is the leading professional organization of stem cell researchers and represents more than 4,000 members in Singapore and around the world. Our members are scientists, clinicians, ethicists, and educators dedicated to the responsible advancement of stem cell research and its translation to the clinic. The ISSCR appreciates that the Bioethics Advisory Committee is evaluating whether MRT should be separated from their 2005 recommendation that clinical research involving heritable genome modifications should not be allowed due to unresolved safety and ethical issues. While we agree with the limitation on heritable nuclear genome editing, we believe that recent scientific advances justify clinical research related to MRT to refine the procedure and assess its safety and efficacy in the context of patients with confirmed mitochondrial disease.

Mitochondrial Replacement Techniques Can Reduce the Transmission of Mitochondrial Disease

New scientific advances make it possible to significantly reduce the transmission of maternally inherited mitochondrial diseases by replacing abnormal mitochondria in a zygote or recently fertilized egg with healthy mitochondria from a donor. It is important to note that cells have two different genomes: the nuclear genome that contains the vast majority of genes and a smaller mitochondrial genome that encodes a small number of the proteins required for energy metabolism. Heritable mitochondrial genome replacement does not involve nuclear genome editing, which remains unsafe because of its potential to unpredictably

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and permanently alter traits involved in many aspects of human physiology. Instead, MRT involves the replacement of pathogenic mitochondrial DNA with healthy mitochondrial DNA, which can be performed safely to prevent the transmission of mitochondrial diseases to children.

Mitochondrial diseases can be devastating for heart, brain, and muscle function. Women carrying a high proportion of mutated mitochondria in their oocytes (eggs) have a higher risk of giving birth to children that may suffer from severe mitochondrial diseases. MRT can significantly reduce their risk of transmitting mitochondrial diseases by replacing the mitochondrial DNA of a mother affected by mitochondrial disease with healthy mitochondrial DNA from a donor, offering parents the opportunity to have healthy children that are biologically related to both parents.

The ISSCR supports enabling clinical research using MRT to prevent the transmission of serious mitochondrial diseases and offered new recommendations for [clinical use of MRT](#) in the society's updated [Guidelines for Stem Cell Research and Clinical Translation](#). The Guidelines recommend limiting the initial uses of MRT to "clinical investigation that is subject to strict regulatory oversight, limited to patients at high risk of transmitting serious mitochondrial DNA-based diseases to their offspring, when no other treatments are acceptable, and where long-term follow-up is feasible" (Guidelines Recommendation 3.4.8.1).

Modernizing Singapore's Approach to MRT

Reflecting recent clinical advances with MRT, several countries have begun to modify their rules to allow clinical investigation of MRT to prevent the transmission of serious mitochondrial diseases. The [United Kingdom](#) became the first country to explicitly allow MRT for this purpose in 2015 and legislation to establish a similar approach to MRT is under consideration by the [Parliament of Australia](#). Enabling clinical research using MRT with a strict regulatory framework to assess its safety and efficacy would be in keeping with these international developments.

Thank you for considering our views as you await the final recommendations of the Bioethics Advisory Committee on MRT. If

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the ISSCR can be of further assistance as you move forward on this issue, please contact Eric Anthony, ISSCR's Director of Policy at eanthony@isscr.org.

Sincerely,

Melissa H. Little
President, ISSCR
Murdoch Children's Research Institute and
University of Melbourne, Australia

Promoting excellence in stem cell science and applications to human health.

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