Mito Foundation position statement on whether mitochondrial donation is distinct from germline genetic modification

This document provides background to international debates and sets out the position of the Mito Foundation on whether mitochondrial donation is distinct from germline genetic modification. This is in response to the Australian Government recommendation for the National Health and Medical Research Council (NHMRC) to advise on this question to inform future legislative processes.

Summary

Mitochondrial donation techniques (being the two specific techniques of Pronuclear Transfer (PNT) and Maternal Spindle Transfer (MST)) should be considered distinct from germline genetic modification for the following reasons:

- The techniques do not *alter* the nuclear DNA which gives rise to physical characteristics and personal traits; and
- DNA is not *modified* during mitochondrial donation – the techniques *replace* the entire faulty mtDNA genome.

The Mito Foundation is only recommending the introduction of mitochondrial donation to enable those families who risk passing on serious mitochondrial disease to have genetically related children free of mtDNA disease.

Mitochondrial donation refers to two specific techniques developed in the UK and USA, which show great potential to avoid the transmission of maternally inherited mitochondrial disease from mother to child. These two techniques, known as Pronuclear Transfer (PNT) and Maternal Spindle Transfer (MST) are summarised here. Both techniques replace abnormal mitochondrial DNA with healthy mitochondrial DNA to avoid serious mitochondrial disease.

Mitochondrial, not nuclear DNA

Mitochondrial donation techniques replace faulty mitochondria with healthy mitochondria from a donor. The Senate Community Affairs Committee indicated that mitochondrial donation does not result in a child having three genetic parents[i] and should be conceptualised in a similar way to organ donation.[ii] The Mito Foundation agrees with this view.

The Mito Foundation also shares the Senate Community Affairs Committee's view that changes to mitochondrial DNA should be considered differently to changes to nuclear DNA due to the role of nuclear DNA in determining physical and personal characteristics. Evidence was presented to the Committee that mitochondrial DNA does not contribute to physical, cognitive or behavioural characteristics other than when faulty mitochondrial DNA causes disease.[iii] Mitochondrial DNA is only responsible for an individual's energy production.

At present, there is no universally agreed definition of 'germline genetic modification'. In the UK, where mitochondrial donation has been legalised, the UK Government determined that, although mitochondrial donation constitutes germline modification, because mitochondrial DNA passes down the maternal female line, it does not constitute germline *genetic* modification.[iv] This was because only mitochondrial DNA is replaced, with nuclear DNA remaining in its original form.

The UK Government thus differentiated mitochondrial donation techniques from those that might alter the nuclear DNA which is responsible for unique personal traits and characteristics.

The Mito Foundation supports the UK Government's approach to this issue and its adoption in Australia.

'Genomic' not 'genetic'

The term "genetics" refers to the study of single genes and this term is appropriate when a specific gene is being targeted or undergoing modification by gene therapy approaches applied to nuclear genes.

Mitochondrial donation is not targeted at a single gene but involves replacement of all the 37 genes comprising the mitochondrial genome. "Genomic" or "genome" is therefore more appropriate terminology to use when describing this process.

'Replacement' not 'modification'

Mitochondrial donation techniques do not modify the DNA, instead replacing the whole (abnormal) mitochondrial genomes with healthy mitochondrial genomes. A number of statements presented during the UK legislative process to permit mitochondrial donation[v] highlight the difference in *replacing* the mitochondrial genome as opposed to *manipulating* or *modifying* it as might occur in gene editing techniques such as TALEN, Zinc Finger or CRISPR/CAS 9 methods. The latter result in new or artificial characteristics which would not occur naturally. Conversely, unique mitochondrial and nuclear combinations result from mitochondrial donation techniques naturally each time an egg is fertilised.

In the US, the Institute of Medicine established a committee to examine the ethical and social policy issues of mitochondrial donation techniques. Working with the Food and Drug Administration, the IoM Committee's established definition of 'genetic modification' concluded that mitochondrial donation techniques do constitute 'heritable germline modification' if used to produce female off-spring as mitochondrial DNA is solely inherited from the mother.[1]

The IoM report goes on to distinguish between modification of mitochondrial DNA to prevent transmission of a disease and modification of nuclear DNA. It noted these distinctions could allow justification of mitochondrial donation techniques independent of decisions about heritable genetic modification of nDNA.[vi]

[1] This definition results in the conclusion that male babies born following mitochondrial donation have not undergone heritable or "germline" replacement since mitochondrial DNA in the sperm will not be passed on to the next generation.

Techniques to avoid 'serious mitochondrial disease'

Mitochondrial donation involves techniques developed to provide families afflicted with maternally inherited mitochondrial disease the opportunity to have genetically related children without serious mitochondrial disease.

If legalised, mitochondrial donation techniques could be an option offered to families to avoid the risk of mitochondrial disease for those people wishing to have biologically related children.

Other countries that have considered the status of MD techniques include the Swedish Council of Medical Ethics in 2013. Although at the time it found the techniques to be ethically unacceptable due to uncertainty regarding safety and efficacy, a majority of the Council thought the techniques would be ethically acceptable if they could be done safely.[vii]

Singapore's Bioethics Advisory Committee released a consultation paper in April 2018 on 'Mitochondrial Replacement Genome Technology'. The paper notes germline modification occurs when 'a gene(s) in a germ cell (sperm or egg) or an early embryo is altered.'[viii] It goes on to describe mitochondrial donation techniques as 'germline modification' but for the same reasons given by the UK Government considers the techniques not to be 'genetic modification'. The paper then focuses on the clinical application of the techniques, highlighting that given scientific developments and international debate it is timely to review the permissibility of 'germline modification' techniques.

Regulatory authorities in the UK, USA, Sweden and Singapore have all recognised that a number of biological and ethical features distinguish mitochondrial donation from germline genetic modification for nuclear gene disorders. The Mito Foundation proposes that the term germline genetic modification is an inaccurate and confusing way to describe mitochondrial donation.

Germline mitochondrial replacement may be a more appropriate description.

---

[i] p 61 *Science of Mitochondrial Donation and Related Matters, Senate Standing Committee on Community Affairs, 27 June 2018 at* https://www.aph.gov.au/Parliamentary_Business/Committees/Senate/Community_Affairs/MitochondrialDonation/Report

[ii] Para 4. 3.1 ibid

[iii] Para 4.22, p 59, ibid

[iv] National Academy of Medicine Committee on the Ethical and Social Policy Considerations of Novel Techniques for Prevention of Maternal Transmission of Mitochondrial DNA Diseases, USA. Mitochondrial Replacement Techniques : Ethical, Social, and Policy Considerations. 2016

[v] p 901, Germline Genetic Modification and Identity: the Mitochondrial and Nuclear Genomes Rosamund Scott and Stephen Wilkinson, Oxford Journal of Legal Studies, Vol. 37, No. 4 (2017), pp. 886–915 accessed at https://academic.oup.com/ojls/article/37/4/886/4082053

[vi] Institute of Medicine: Report in Brief: Mitochondrial Replacement Techniques: Ethical, Social, and Policy Considerations p2 accessed at http://www.nationalacademies.org/hmd/~/media/Files/Report%20Files/2016/Mitochondrial%20Replacement%20Techniques/MitoEthics-RIB.pdf

[vii] The Swedish National Council on Medical Ethics, Sweden. Summary : Mitochondria Replacement in Cases of Serious Diseases — Ethical Aspects. 2013. See p5 accessed at http://www.smer.se/wp-content/uploads/2013/11/Mitochondria-replacement-sammanfattning-eng2.pdf

[viii] Singapore Bioethics Committee Consultation Paper April 2018, p 7 accessed at https://www.reach.gov.sg/participate/public-consultation/bioethics-advisory-committee/public-consultation-on-ethical-legal-and-social-issues-arising-from-mgrt