MONASH University

MONASH BIOMEDICINE DISCOVERY INSTITUTE

11th May, 2018

Jeanette Radcliffe
Secretary, Senate Community Affairs References Committee
Parliament House
PO Box 6100, Canberra 2600

Dear Ms Radcliffe,

Re: Inquiry into the Science of mitochondrial donation and related matters

This submission was prepared by Prof. John Carroll and Prof. Mike Ryan on behalf of the Monash Biomedicine Discovery Institute, Monash University.

Prof. John Carroll is Director of the Monash Biomedicine Discovery Institute at Monash University. He has a long standing research program in the development of eggs including their maturation and fertilization. Through this, he has studied various aspects of mitochondrial activity in oocytes with the aim of improving oocyte quality. He collaborates with various researchers and clinicians including from Monash IVF as well Prof. Mary Herbert at the Wellcome Centre for Mitochondrial Research at Newcastle University (UK) who is the world leader in mitochondrial donation therapy.

Mike Ryan is a Professor in biochemistry and molecular biology at the Monash Biomedicine Discovery Institute and Associate Dean of Research in the Faculty of Medicine at Monash University. Over the past 15 years, he has conducted research into mitochondrial biology and disease. The main focus has been on the characterization of cellular and mitochondrial defects that result from gene mutations identified in patients. A significant aspect is understanding the interplay between the products from nuclear and mitochondrial DNA. Prof. Ryan has received funding from the NHMRC to conduct this work and has had a long standing collaboration with Prof. David Thorburn at the Murdoch Childrens Research Institute. He also collaborates with many other national and international researchers. This includes with researchers from the Wellcome Centre for Mitochondrial Research at Newcastle University (UK), but not related to mitochondrial donation. Prof. Ryan is a member of the Scientific and Medical Advisory panel of the Australian Mitochondrial Disease Foundation (AMDF).

Professors Carroll and Ryan were among 40 international researchers who were co-signatories to a letter in The Guardian (UK) in 2015 urging the UK Parliament to approve the proposed regulations for mitochondrial donation. They have advocated mitochondrial donation for mtDNA mitochondrial disease at community meetings and through discussion with their local MPs.

Particular aspects related to the terms of reference are addressed below.

(a) the science of mitochondrial donation and its ability to prevent transmission of mitochondrial disease;

ATP (adenosine triphosphate) is a molecule found in our cells and acts like a battery pack to drive non-spontaneous chemical reactions – this includes the movement of muscle fibres, triggering of neurons, beating of the heart. We are constantly using ATP and need to replenish it by burning the fuels we eat. About 20% of all ATP is used by the brain, even though this organ is about 2% of total body weight.

Almost all of our ATP is made in mitochondria – small but abundant compartments found in our cells. The machinery that makes ATP in mitochondria requires genes found in both nuclear DNA and mitochondrial DNA (mtDNA). Mutations in these particular genes can lead to the ATP generating machines not working properly thereby leading to mitochondrial disease.

mtDNA is passed down to the next generation exclusively through the mother. This is because the egg is packed with mitochondria and contains about 200,000 copies of mtDNA. The sperm contains only a few copies of mtDNA and these are degraded after fertilization. Therefore, mtDNA mutations, if present in eggs, can be inherited down the maternal line to the offspring. When there are sufficient mutant copies of mtDNA in the egg, this can lead to mitochondrial disease.

Mitochondrial donation, or mitochondrial replacement therapy, involves transplantation of nuclear DNA from the affected mother's egg to an enucleated egg from a healthy donor. Two mitochondrial donation techniques have been extensively investigated - (1) spindle transfer and (2) pronuclear transfer. The result of the mitochondrial donation procedure is the generation of an embryo containing healthy mtDNA thereby preventing the transmission of mitochondrial disease. It should be noted that the embryo will contain the nuclear DNA from the mother and father along with mtDNA from the donor. The nuclear DNA contains all of the genes that confer an individual's uniqueness – such as physical appearance. The donor mtDNA only corrects defects related to energy generation.

(b) the safety and efficacy of these techniques, as well as ethical considerations;

The application of any new procedures to a patient population does not come without some level of risk. However, the risk needs to be balanced with the potential therapeutic benefits. Given the existing evidence, we believe that the benefits of mitochondrial donation therapy outweigh the risks.

Mitochondrial donation approaches have been successfully applied in rodent models, non-human primates (macaque monkeys) and most recently in human embryos. The micromanipulation techniques have been established for several decades. Australia has been at the forefront of reproductive technologies since the advent of IVF and hence mitochondrial donation approaches are well within our capabilities and expertise.

Extensive debate has been conducted in the UK regarding the analysis of safety, efficacy and ethics of mitochondrial donation therapy. As a result, legislation for mitochondrial donation therapy was successfully introduced in the UK. A code of practice towards the implementation of mitochondrial donation has been published (https://www.hfea.gov.uk/code-of-practice/33#section-header). This provides a clear framework that we believe can be adapted for use in Australia.

(c) the status of these techniques elsewhere in the world and their relevance to Australian families;

Both spindle transfer and pronuclear transfer techniques have been shown to be valid approaches to mitochondrial donation therapy[1]. The Wellcome Centre for Mitochondrial Research at the University of Newcastle (UK) has pioneered and optimized the pronuclear transfer technique to ensure that transfer of mutant mtDNA is below levels that are likely to cause mitochondrial disease in offspring[2]. An alternative approach involving spindle transfer was successfully adopted in rodent and non-human primate (macaque) models. More recently this approach was employed by a group in US/Mexico who reported the first case of mitochondrial donation therapy in humans[3]. While serious reservations exist in regards to the ethical and regulatory process, the successful outcome of an apparent healthy baby with sub-threshold mtDNA mutant load has demonstrated the feasibility of this technique.

The relevance and application of these techniques to Australian families with mitochondrial DNA disease is indisputable. Moreover, our close collaborative links with the Wellcome Centre for Mitochondrial Research at the University of Newcastle will provide us with the most up-to-date approaches regarding the implementation of mitochondrial donation therapy for translation into the Australian setting.

(d) the current impact of mitochondrial disease on Australian families and the healthcare sector;

We acknowledge the outstanding work performed by the Australian Mitochondrial Disease Foundation (AMDF) and direct you to their submission.

(e) consideration of changes to legal and ethical frameworks that would be required if mitochondrial donation was to be introduced in Australia;

We understand that changes to federal and state legislation will be required to adopt mitochondrial donation therapy and we believe that this is fully justified given the impact of mitochondrial genetic disease on Australian families. An appropriate framework should be adopted with a code of practice that limits mitochondrial donation therapy to a small number of approved clinics. This takes into account the relative size of Australia's population and demand for the approach, as well as the technical expertise required to successfully undertake the technique.

(f) the value and impact of introducing mitochondrial donation in Australia; and

The prevention of mitochondrial DNA disease through mitochondrial donation will undoubtedly reduce the burden on Australia's healthcare system and greatly alleviate the emotional and financial pressures on families affected by the disease.

We are also aware of mitochondrial donation therapy being offered in IVF clinics in countries without clear regulatory oversight. Should Australia not legislate mitochondrial donation therapy, parents seeking such approaches may be forced to seek procedures in these unregulated environments.

In closing, we are strongly supportive of mitochondrial donation therapy being approved within Australia. Given the precedent in the UK as well as Australia's proven expertise in clinical genetics related to mitochondrial disease and pioneering approaches to IVF technologies, we are ideally placed to undertake mitochondrial donation therapy for the benefit of Australian families with mitochondrial disease.

We thank the Senate Community Affairs Reference Committee for their involvement and providing us with the opportunity to make a response.

Prof. John Carroll

Prof. Mike Ryan

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References

1. Herbert M and Turnbull D Progress in mitochondrial replacement therapies. Nat. Rev. Mol. Cell Biol. 19, 71-72.

2. Hyslop LA, Blakeley P, Craven L, et al. Towards clinical application of pronuclear transfer to prevent mitochondrial DNA disease. Nature 2016;534:383-386.

3. Zhang J, Liu H, Luo S, et al. Live birth derived from oocyte spindle transfer to prevent mitochondrial disease. Reproductive biomedicine online 2017;34:361-368.