

Nuffield Council for Bioethics: Emerging techniques to prevent inherited mitochondrial disorders: ethical issues

Response by the Medical Research Council and the Wellcome Trust

March 2012

1. The Medical Research Council (MRC) and the Wellcome Trust (the Trust) are pleased to respond to the Nuffield Council of Bioethics call for evidence for 'Emerging techniques to prevent inherited mitochondrial disorders'.
2. As funders of important research into understanding mitochondrial DNA ('mtDNA') and more specifically techniques to prevent inherited mitochondrial disorders, we are committed to ensuring that sufferers of mitochondrial disorders can benefit from the outputs of our research.
3. The impact of mitochondrial disorders is broad ranging and in severe cases can lead to miscarriage/still birth, early infant death, or chronic illness in later life. Research in this field is therefore important in advancing our knowledge, not only to avoid the transfer of such diseases but also to develop treatments for those, often very young, patients who currently suffer from the diseases.
4. We encourage discussion, deliberation and debate of ethical issues around emerging techniques to prevent inherited mitochondrial disorders. We believe that if research indicates that such techniques are likely to be effective, there will be compelling ethical reasons for permitting their use – thus, enabling women who carry mitochondrial disease to choose to have children unaffected by these devastating disorders.
5. It has been argued that the two techniques currently in question could raise different ethical issues and so one or other should be prioritised for scientific investigation. The nature of science is such that avenues to explore both techniques need to remain open so that the efficacy and safety of each technique can be compared. Furthermore, exploration of each technique has and will lead to insights into mitochondria and developmental biology which will benefit other areas of research.
6. **Background: The importance of research into mitochondria:** Mitochondrial DNA is present in practically every cell in the body. Mitochondrial genetic defects can cause multisystem disorders. Abnormal mtDNA is present in about 1 in 250 live births. Although many of these cases will not result in significant symptoms, at least 1 in 10,000 adults in the UK are severely affected by mitochondrial disease. Researchers at Newcastle University currently care for over 400 patients with mitochondrial disease. Research on this cohort of patients has highlighted the following issues:
 - a. 50-60% of all children with mitochondrial disease do not have a genetic diagnosis and 40% of these children have a generalised defect of mtDNA expression. Being able to establish the genetic basis in these patients will enable specific genetic advice and the ability to suggest new approaches to treatment;
 - b. There is currently no cure for mitochondrial disease. Whilst some patients are able to lead almost normal lives with relatively low levels of symptoms, for women of child-bearing age, carrying mtDNA mutations will significantly impact on their ability to have an unaffected child.

7. Advances in scientific knowledge have put researchers in a strategic position of being able to utilise insights into mitochondrial DNA and techniques from in-vitro fertilisation to develop the concept of preventing transmission of mutated mitochondrial DNA. Women with mtDNA mutations are at risk of passing on these mutations to their children. Such women have a number of reproductive options open to them, including genetic counselling, *in utero* testing, egg donation, and pre-implantation diagnosis. Increasingly women are opting for such early diagnosis. This option however is not suitable for women with high levels of heteroplasmic or homoplasmic mtDNA mutations.¹
8. The principle of preventing transmission of mutated mtDNA by transplanting the nuclear genome in embryonic cells in early stages has been successfully demonstrated in animal models and recently shown to work in abnormal human zygotes.
9. **Further research:** The Wellcome Trust recently announced a £4.4 million strategic award to Professor Doug Turnbull and his research group at Newcastle University to undertake a programme of work on mtDNA expression, disease and treatment. A component of this award will focus on further developing two techniques as options to prevent the transfer of diseased mtDNA.
10. This work was considered by the Human Fertilisation and Embryology Review Panel in February 2011. The panel concluded that 'the techniques of maternal spindle transfer and pronuclear transfer are potentially useful for a specific and defined set of patients whose offspring may have severe or lethal genetic disease and who have no other option of having their own genetic child'. The panel recommended that additional studies be undertaken both on basic research to improve the knowledge about the biology of human mitochondria and on research aimed specifically at providing further safety information on Maternal Spindle Transfer ('MST') and Pro-Nuclear Transfer ('PNT').
11. The panel further proposed a minimum set of critical experiments to be undertaken before these techniques could be considered safe and effective for clinical use. These are as follows:
 - a. MST using human oocytes that are then fertilised (not activated);
 - b. PNT using normally-fertilised human oocytes and development compared to normal ICSI-fertilised human oocytes;
 - c. PNT in a non-human primate model, with the demonstration that the offspring derived are normal.
12. Work on the first two recommendations will be covered under the current award to Newcastle University.
13. This consultation proposes that treatment will still be in its experimental phase when offered in the clinic. The research to be undertaken under the current award to Newcastle University is to continue to test the safety and efficacy of the techniques and such techniques would not and should not be approved for use in the clinic until the scientific evidence exists to show it is as safe as can reasonably be proven in laboratory and/or animal models to use in women. Indeed, there will be significantly more evidence available on the safety of this technique before its use in the clinic than was available

¹ McFarlane R, Clare KM, Morris AA, Taylor RW, Macphail S, Lightowlers RN, Turnbull DM. Multiple neonatal deaths due to a homoplasmic mitochondrial DNA mutation. *Nat Genet* 2001;30:145-6.

when other assisted reproduction therapies, such as IVF, were first introduced. It must be acknowledged, that no new technique can ever be deemed to be 100% safe before using in humans. The first IVF techniques had to be tested in human patients once shown to be safe in the laboratory.

14. We do not believe the transfer of mtDNA raises issues around identity, since it does not carry any genetic data associated with the normally accepted characteristics of identity. An analogy could be drawn with replacing the battery in a camera-the brand of the battery does not affect the functioning of the camera.
15. We acknowledge that the transfer of mtDNA differs from other medical transplants in that it will affect every cell in the body, and females born this way are likely to transmit their altered mtDNA to future generations. We do not believe that this raises unacceptable ethical concern, because 'natural' mtDNA that is not altered using this technique would be deleterious to those future generations. We believe most families affected by mitochondrial disorders will consider it desirable that the technique will protect not only their children, but their grandchildren as well.
16. This consultation asks whether the use of pre-implantation sex selection by patients who might use these techniques is reasonable. This would seem to raise different ethical issues from those involved in deciding whether techniques for preventing transmission of mitochondrial disorders are ethically acceptable.
17. **Guidelines:** Should these techniques be introduced into the clinic, then we would expect best practice guidelines, similar to those that currently apply to IVF to also apply to these techniques and to donors. Unlike sperm and egg donations, we would suggest that details regarding the donor should remain anonymous in view of our position relating to identity as above.
18. Data, including identification of donor should be kept, however, for longer-term follow up and may be of longer-term medical utility. It will be crucial to ensure that a robust mechanism is in place for long-term follow up of any children born following use of these techniques.
19. **Not treating:** Medical knowledge in this field has reached this current stage of advancement as a result of world leading research which has been funded through public and charitable funders. It would seem a difficult position, if techniques which are developed and shown to be safe, could not be offered to women to enable them to have children free of devastating mitochondrial diseases. We welcome this review by the Council to help inform funding decisions, as ultimately we wish to invest in research that will be translatable into clinical practice for patient benefit.

The Medical Research Council (MRC) is one of the main agencies through which the UK Government supports medical and clinical research. The MRC is dedicated to improving human health through the best scientific research. Funded by the Department for Business, Innovation and Skills (BIS), the MRC's work ranges from molecular level science to public health medicine and has led to pioneering discoveries in our understanding of the human body and the diseases which affect us all. This evidence is submitted by the Medical Research Council (MRC) and represents the independent views of the research council. It does not include or necessarily reflect the views of the other UK research councils, Research Councils UK or the Department for Business, Innovation and Skills