

Briefing paper on the need to protect the future possibility of treating mitochondrial disease and other conditions by a procedure that involves mitochondrial transplantation.

Prepared by

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Context:

Human Fertilisation and Embryology Bill: Part 1-Amendments of the Human Fertilisation and Embryology Act 1990

Summary:

Mitochondria are tiny energy-producing structures vital to cell function. The mitochondria are transmitted to the next generation through the egg cytoplasm, but not via the sperm, so mitochondrial defects are only inherited from the mother. Innovations in embryology raise realistic hopes for preventing some mitochondrial disorders being passed on to a child by transplanting healthy mitochondria to replace dysfunctional ones.

It may be some time before mitochondrial transplantation becomes firmly integrated as a therapy, but the science is already well advanced. The Embryology Bill must take account of this likely development and leave the decision on whether it is safe and effective to license such treatment to the HFEA.

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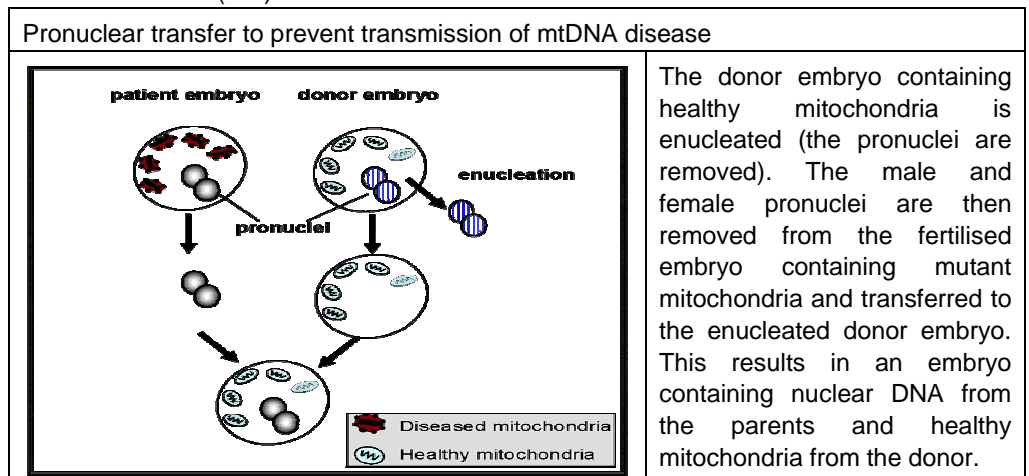
(2) Background – Mitochondrial Disease

Mitochondrial disorders are a cruel class of inherited disease, because serious, even life-threatening conditions are coupled with great unpredictability about how future children will be affected. Mitochondrial disorders can include fatal liver failure, stroke-like episodes, mental retardation with intractable epilepsy, muscle weakness, diabetes and deafness.

All cells of the body have many (typically 1000-10,000) mitochondria in the cytoplasm that surrounds the nucleus. Mitochondria are tiny energy-producing structures ('organelles') vital to cell function. If they malfunction then organs will eventually fail. The mitochondria are transmitted to the next generation through the egg cytoplasm, but not via the sperm, so mitochondrial defects are only inherited from the mother.

Many mitochondrial disorders are not inherited in the usual sense of there being a defective gene ('mutation') in the regular human genome. Mitochondria carry their own DNA that is only 0.0005% the length of the nuclear human genome. It contains just 37 coding genes (0.15% of human genes), but harmful mutations can occur within them. Evolutionarily, mitochondria are enslaved primitive bacteria with their own genetic code. They replicate independently of the nucleus and carry no information that defines any human attribute. Mitochondrial DNA is less stable than nuclear DNA, so it varies greatly both between and within species. While this variation is frequently used in studies of evolution and to help classify individuals or their remains, this variation is not within genes that define any species characteristic.

The seriousness of the disease depends on the proportion of mutant mitochondria. A woman carrying some mutant mitochondria puts *all* of her potential children at risk of serious disease. The proportion of mutant mitochondria varies from cell to cell, so sadly prenatal diagnosis or pre-implantation genetic diagnosis may have limited value to relieve her terrible uncertainty of whether her baby will be seriously affected or less so. The only prospect such women have of conceiving their own unaffected, genetic children is through the development of mitochondrial (cytoplasmic) transplantation therapy in association with *in vitro fertilisation* (IVF).



Previous research in mice has shown this approach is feasible and successful in preventing transmission of mitochondrial disease.¹

In summary, there is a need for this research to progress to therapeutic application. The disorders are serious, sometimes life threatening.

¹ Sato A, Kono T, Nakada K et al. Gene therapy for progeny of mito-mice carrying pathogenic mtDNA by nuclear transplantation. Proc Natl Acad Sci U S A. 2005;102:16765-16770

(3) The legal situation

The existing 1990 Human Fertilisation and Embryology Act permits just *laboratory* research into human cytoplasmic transplantation. Such a research has been conducted at NESCI under licence by the Human Fertilisation and Embryology Authority since 2005 (R0153) and the laboratory studies are on-going.

In Clause 3, 'Prohibition in connection with embryos', the proposed Human Fertilisation and Embryology Bill **allows** Regulations to be introduced in the future in respect of the clinical application of this research to prevent the transmission of mitochondrial disease.

The **current wording** in the Bill:

"(5) Regulations may provide that—
(a) an egg can be a permitted egg, or
(b) an embryo can be a permitted embryo,
even though the egg or embryo has had applied to it in prescribed
circumstances a prescribed process designed to prevent the transmission of
serious mitochondrial disease." (our emphasis)

This 'amber' signal is welcome,

YET **Making clinical treatment subject to Regulations is likely to cause
delays in introducing research advances into clinical practice.**

Indeed, such regulation-making powers are sometimes never utilised. Political considerations, personnel changes, and busy timetables can easily lead to a situation where questions of seemingly complicated science are delegated to the bottom of policy-makers agendas.

INSTEAD **The decision to introduce this technique as a clinical treatment
should be based on whether researchers can produce convincing
evidence of safety and efficacy to the HFEA.**

The discretion to grant a licence for a new clinical treatment involving embryos and gametes ordinarily rests with the HFEA. Likewise, there is a case for the HFEA to be allowed to determine whether or not to licence cytoplasmic transplantation. The Authority has been overseeing and regulating developments in this area for many years. It will be ideally placed to assess the safety and efficacy of each particular case and incorporate detailed scrutiny by members of the scientific community with appropriate expertise.

The following **AMMENDMENTS** were proposed by Mark Simmonds and Andrew Lansley

- ✓ Clause 3, page 3, line 7, at the end insert 'except when the egg has in prescribed circumstances undergone a prescribed process designed to prevent the transmission of serious or life-threatening mitochondrial diseases.'
- ✓ Clause 3, page 3, leave out lines 19 to 24

The first amendment incorporates the Lord's amendment and intention, removes the legislative obstacle of further regulations and makes mitochondrial transplants licensable under the scrutiny of the HFEA. The second amendment is housekeeping by removing the then-redundant other provision.

**In the interest of medical science, we hope that the above amendment
will be accepted by the whole House**

(4) Policy and ethical concerns

The above clearly highlights the compelling scientific and medical case for continuing research on mitochondrial transplants. Questions arise if there are ethical concerns that stand against the possible use of this technique in treatment.

Will the child have 'three parents'? – The idea that the resulting child has 'three parents' is not tenable. As indicated above the DNA in mitochondria carries no information that defines any human attributes, so it cannot be 'parental' in any significant way. Such organelle transplantation could be viewed in the same way as kidney transplants or blood transfusions which also involve transferring a small amount of genetic material from a third person.

Will this legalise human cloning? – The technique outlined here is not the same as reproductive cloning. Reproductive cloning describes the situation where any baby created would be genetically identical to a donor by transferring a nucleus from that donor into an enucleated egg. Reproductive cloning is, and will remain, illegal in the UK. In mitochondrial disease treatment the exact opposite occurs – a transfer of the *cytoplasm* (and with it normal mitochondria) from the donor. It happens to be technically easier to remove the nuclear DNA from the donor egg and to transfer the desired egg- and sperm-derived pronuclei from a fertilised egg into this cytoplasmic bag than to suck the cytoplasm out of the mother's egg and replace it with cytoplasm taken from the donor egg. A key feature of cloning is that the donor nucleus from a somatic cell (e.g. a skin cell) is 'reprogrammed' back to an embryonic, state. Mitochondrial disease treatment does not involve such remodelling.

Is it the same as germline gene therapy? – Germline gene therapy is a term used for modifying genes in the *nuclear* genome at the beginning of development with the intention of changing the organism in a specific way and for potentially transmitting this change to subsequent progeny. Due to the complexity of the nuclear genome, there are risks associated with modifying it, thus only gene therapy that avoids the germline is currently permitted. Replacing diseased mitochondria with healthy ones is an inherently less complicated procedure. No genome is being modified. Whole mitochondria are being replaced. It is true that once normal mitochondria are in place, the subsequent generations will have normal mitochondria too - hardly a bad thing.

Are there other ways of dealing with this? – Ovum donation may be unacceptable to some couples since it does not permit them to have genetic children of their own. The options of prenatal diagnosis or pre implantation genetic diagnosis are not available or appropriate for many women – especially if there are ethical concerns about discarding or destroying a fully formed embryo after it was formed. Also, in some situations, mitochondrial donation may be the only available medical alternative.

In summary: on closer consideration the ethical 'talking points' regarding this technique do not stand up to scrutiny. In fact, a compelling moral case can be made for removing all bureaucratic obstacles that prevent the reliance on mitochondrial donation where it is considered safe and effective.

(5) Further information

This brief has aimed at presenting the perspective of scientists and clinicians on the proposed legislation in a succinct and simple manner.

We would greatly welcome a chance to explain the underlying science and the therapeutic potential in greater detail. Please do not hesitate to contact us with any further questions or comments.

The North-East England Stem Cell Institute, a collaboration between the Universities of Durham and Newcastle, the Newcastle upon Tyne Hospitals NHS Foundation Trust and other regional partners.

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