Institution: Newcastle University

Unit of Assessment: UoA-1

Title of case study: Towards prevention of mitochondrial diseases: changing government policy and influencing public debate.

1. Summary of the impact

Research at Newcastle University, the only centre licenced in the UK, has shown that the *in vitro* fertilisation-based technique of pronuclear transfer to prevent the transmission of mitochondrial disease from mother to child is feasible. As a consequence the UK Government asked the regulator responsible, the Human Fertilisation and Embryology Authority (HFEA), to conduct both a scientific safety review of the techniques in which Newcastle research was widely referenced and to undertake a public consultation exercise. The findings from both these consultations and from a separate Nuffield Council on Bioethics report were supportive, to the extent that in June 2013 the UK's Chief Medical Officer announced that the Government would bring forward draft legislation to change the law in the UK to allow embryos created using the Newcastle approach to be used for the treatment of affected couples.

2. Underpinning research

Key researchers.

Professors Mary Herbert and Douglass Turnbull of Newcastle University led the research on pronuclear transfer (PNT). Professor Alison Murdoch of the Newcastle Fertility Centre led the clinical care of the women who donated eggs. Professor Patrick Chinnery studied the likelihood of intergenerational transfer of diseased mitochondria after PNT.

Background.

Mitochondria provide about 90% of the body's energy requirements and are the only cellular structures other than the nucleus that contain DNA. Each mitochondrion contains multiple copies of this DNA and each cell has many mitochondria.

Mitochondrial diseases result when mitochondria do not function correctly and many arise because of mutations in the mitochondrial DNA. Mutations may arise spontaneously or be inherited and may affect all or only some of the mitochondria. Inherited mitochondrial diseases pass down the female line only, since all the mitochondria of a new embryo derive from those present in the egg cell. The incidence of early onset mitochondrial disease is 1 in 16,129 births per year (Sklaldal et al. 2003 PubMed ID: 12805096) implying around 50 new cases per year in the UK. Research in Newcastle on the prevalence of mitochondrial DNA disease in adults indicated a minimum prevalence of 1 in 10,870 meaning that more than 4,600 people are living with such disease in the UK (R1). There are no effective treatments available for mitochondrial disease, which can result in serious medical conditions, including blindness, heart failure, liver failure, learning disabilities and diabetes. Many conditions lead to death in early infancy. Genetic advice to affected couples planning a family is difficult because of the variable nature of the severity with which many such diseases affect individuals.

In vitro fertilisation is a technique developed to help couples who, for whatever reason, cannot conceive. It involves hormonal stimulation of the ovaries and surgical retrieval of eggs. Fertilisation is then attempted *in vitro*. Fertilised eggs are cultured for a few days before the highest quality embryos are transferred to the woman in the hope of establishing a pregnancy.

The legal position on research on sperm, eggs and embryos in the UK is dictated by the Human Fertilisation and Embryology Act (1990), amended in 2008. All research must be licensed by the HFEA. The UK approach to regulation of research on human embryos has been adopted by many countries around the world.

Approaches to preventing the transmission of mitochondrial disease

There are two approaches that show promise to prevent the maternal transmission of mitochondrial disease to offspring. Both involve transferring the human genome of the parents into a donated egg that contains a healthy mitochondrial genome. Maternal spindle transfer (MST) is an

approach in which the chromosomes from the egg of a woman with mitochondrial disease are transferred to a donor egg from which the chromosomes have been removed. The egg is then fertilised to provide the paternal contribution to the offspring's genome (Tachibana et al. 2013 PubMed ID: 23103867). Pronuclear transfer (PNT) involves removing the maternal and paternal genomes (pronuclei) from the patient's egg that has been fertilised *in vitro* and placing them into a donor egg that contains only the mitochondria of the donor (an enucleated egg) (McGrath and Solter 1983 PMID: 6857250). Both approaches result in offspring that are genetically identical to an embryo that would arise from normal fertilisation, but that no longer carry a dysfunctional mitochondrial genome.

Newcastle is the only centre in the UK licenced to conduct research that addresses the safety and efficacy of PNT.

Work by others (McGrath and Solter 1983 PMID: 6857250) using mice had shown that transfer of pronuclei from one egg to another immediately after in vitro fertilization led to normal development to adulthood and ensuing fertility in offspring. It was later shown, again in the mouse, that signs of mitochondrial disease could be safely eradicated by transferring the pronuclei from the disease-affected fertilised egg to an egg with healthy mitochondria, from which nuclear DNA had been removed (Sato, et al. 2005 PMID**:** 16275929).

Newcastle research

Newcastle researchers wished to test the technical feasibility of pronuclear transfer in humans. This was a challenge because the pronuclei of human eggs are several times larger than those of mouse eggs and therefore required new transfer techniques to be developed to avoid damage to the egg's plasma membrane. In 2005 they were granted a licence by HFEA to carry out the work. The study used abnormally fertilised eggs obtained with consent from a donor, a patient undertaking in vitro fertilisation. A new method of introducing the pronuclei into the recipient eggs was developed and shown to be successful, in that eggs with transplanted pronuclei developed normally to blastocysts (the latest developmental stage at which they can legally be kept in the laboratory in the UK). Thus the Newcastle research demonstrated the feasibility of PNT in humans (R2).

The carry-over of mitochondria from the disease-affected egg to the healthy egg along with the pronuclei was a major concern in the development of the technique, as it was possible that damaged mitochondria might be transmitted across generations. Further Newcastle-led research has determined that this is unlikely (R3).

3. References to the research

(Newcastle researchers in bold. Citation counts from Scopus as at July 2013.)

R1. **Schaefer AM, McFarland R, Blakely EL, He L, Whittaker RG, Taylor RW, Chinnery PF, Turnbull DM**. (2008) Prevalence of Mitochondrial DNA Disease in Adults. *Annals of Neurology* 63, 35–39. doi: 10.1002/ana.21217 **Cited by 154.**

R2. **Craven L, Tuppen HA, Greggains GD, Harbottle SJ, Murphy JL, Cree LM, Murdoch AP, Chinnery PF, Taylor RW, Lightowlers RN, Herbert M and Turnbull DW**. (2010) Pronuclear transfer in human embryos to prevent transmission of mitochondrial DNA disease. *Nature*, 465, 82–85. doi**:** 10.1038/nature08958 **Cited by 61.**

R3. Samuels DC, Wonnapinij P and **Chinnery PF**. (2013) Preventing the transmission of pathogenic mitochondria DNA mutations: can we achieve long-term benefits from germ-line transfer? *Human Reproduction* 28(3) 554-9. doi: 10.1093/humrep/des439 **Not yet cited**

Key funding

Project Grant- Muscular Dystrophy Campaign. Mitochondrial DNA disorders: is there a way to prevent transmission? 01/01/2005 – 30/09/2008 (PI: Professor DM Turnbull) £166,896

Project Grant- Muscular Dystrophy Campaign. Mitochondrial DNA Disorders: is there a way to prevent transmission? 01/10/2008 – 31/05/2012 (PI: Professor DM Turnbull) £199,993

4. Details of the impact

The Newcastle research demonstrating the feasibility of preventing the transmission of mitochondrial disease using PNT has led to a chain of impacts in the spheres of public policy and public debate resulting in a Government commitment to change the law in the UK.

The Human Fertilisation and Embryology Act 1990 (as amended in 2008), only permits eggs and embryos that have not had their nuclear or mitochondrial DNA altered to be used for treatment. However, the Act allows for regulations to be passed by Parliament that will legally allow such alterations in order to prevent the transmission of serious mitochondrial disease. The sequence of events leading to the proposed introduction of these regulations, on which Newcastle research and researchers had an impact, is outlined below.

Impacts on public policy debates: the regulator.

In 2005 the regulator (the HFEA) licensed Newcastle researchers to conduct research: *Mitochondrial DNA Disorders: Is there a way to prevent transmission?* (EV a) and in April 2010 the results of research on pronuclear transfer were published online in *Nature* [R2]. The Parliamentary Under-Secretary of State for Health, in a 2013 debate, noted, '*In 2010, Newcastle researchers approached the Department of Health and, in the light of their progress, requested that we consider introducing regulations to allow mitochondria replacement in treatment.'* (EV b). As a consequence of this, the HFEA *Scientific and Clinical Advances Advisory Committee* met in May 2010 to consider developments and Newcastle researchers were invited to present evidence (EV c). In February 2011 The Secretary of State for Health asked the HFEA to carry out a formal scientific review and in April 2011 they reported (EV d). Newcastle provided two of only seven experts who were invited to give evidence. The review recommended a minimum set of experiments that were critical to a decision about the safety of the methods, including work on PNT in both humans and non-human primates. As a consequence of R2, the human PNT research on normally-fertilised oocytes formed a substantial part of the research plan for the Wellcome Trust Mitochondrial Research Centre, established in Newcastle in April 2011. This work and the analysis in R2 were reported to the HFEA *Scientific and Clinical Advances Advisory Committee* in 2013, Professors Turnbull, Herbert and Murdoch having been invited to participate in the first core panel meeting (EV d). As a result of this research and that of others showing a lack of success of PNT in macaque monkeys, the Committee removed the requirement for further work in non-human primates in 2013 (EV d contains both the 2011 and 2013 findings).

Meanwhile, in June 2011 the *HFEA Ethics and Law Committee* considered the ethical and legal aspects of PNT and MST to combating mitochondrial disease. The result of this was a paper, published in 2012 and incorporating information derived from Newcastle research, which was circulated to inform debate and discussion within the HFEA and more broadly among external stakeholders (EV e).

Impact on society: Consultation exercises stimulate public debate 2012-13.

In January 2012 the Secretaries of State for Health and for Business, Innovation and Skills jointly asked the HFEA to seek public views on new techniques to prevent the transmission of mitochondrial disease. The public consultation ran from July – December 2012 and the final report noted that 90 participants engaged in deliberative workshops and that other activities, including schools events, engaged with at least 2,967 members of the public (EV f).

January 2012 also saw the Nuffield Council on Bioethics open a call for evidence that ran through January and February 2012 for a report on the ethics of novel techniques to prevent mitochondrial diseases. In total, 92 organisations and individuals contributed evidence and several Newcastle researchers are cited in the full report, published in June 2012 (EV g).

Impact on Parliamentary debate.

In March 2013 the Parliamentary Office for Science and Technology published a POSTNote (an accessible review for Parliamentarians) on new techniques for preventing mitochondrial disease. This referenced both the Newcastle Nature paper (R2) and the Nuffield Council on Bioethics report to which Newcastle researchers contributed (EV h).

The issues raised in the various sources of information and advice given to parliamentarians were

aired in a Westminster Hall adjournment debate in June 2013, initiated by a Newcastle MP. In the debate, the Parliamentary Under-Secretary of State for Health said,

> *I pay great tribute to researchers at the International Centre for Life in Newcastle* [the building in which the PNT research takes place] *… it is a fine institution. They have been developing their groundbreaking expertise for many years. In anticipation of significant advances in this field, the Human Fertilisation and Embryology Act 1990 was amended in 2008 to introduce a regulation-making power that, if implemented, would enable mitochondria replacement to take place in treatment.* (EV b, col: 64.)

The Parliamentary Under-Secretary of State for Health went on to make clear that the Government would consider the issue, led by the Chief Medical Officer. The decision was announced in late June 2013 that draft legislation that will be brought forward to permit the use of PNT in treatment. The Chief Medical Officer noted that about 10 families each year could be affected and said,

> *Scientists have developed ground-breaking new procedures which could stop these diseases being passed on, bringing hope to many families seeking to prevent their future children inheriting them. It's only right that we look to introduce this life-saving treatment as soon as we can.* (EV i)

Newcastle University researchers, as the only group in the UK licensed to conduct PNT research have thus been at the heart of developments in public policy and law in what remains a challenging and ethically sensitive research area.

5. Sources to corroborate the impact

EV a. Documentary evidence: HFEA reference R0153. Both a lay summary and further details of the licensed research, together with details of how the licence was granted, are available at http://www.hfea.gov.uk/1564.html

Ev b. Hansard record of Westminster Hall debate. (HC Deb 4 25 Jun 2013, vol 565, part 23 Cols 60WH – 67WH). The first quote is in Column 65WH, the second in Col 64WH. Available at: http://www.publications.parliament.uk/pa/cm201314/cmhansrd/cm130625/halltext/130625h0002.htm#13062568000002

Ev c. Documentary evidence: HFEA. Scientific and Clinical Advances Advisory Committee meeting minutes, 2010. Available at http://www.hfea.gov.uk/5906.html

Ev d. Documentary evidence: HFEA. *Review of scientific methods to avoid mitochondrial disease 2011 (including 2013 update).* The documents available at the following link cite evidence supplied by Newcastle researchers and include the HFEA *Scientific reviews of 2011 and 2013 and the Core panel meeting: non-confidential minutes* (2013) referencing R2 above. Available at http://www.hfea.gov.uk/6372.html

Ev e. Documentary evidence: HFEA, Ethics and Law Advisory Committee paper. Available at http://www.hfea.gov.uk/ELAC-November-2012.html

Ev f. Documentary evidence: HFEA and Office for Public Management. Information on the public consultation (launch, methodology and findings) can be accessed at http://www.hfea.gov.uk/6896.html

Ev g. The Nuffield Council on Bioethics report can be accessed at http://www.nuffieldbioethics.org/publications

Ev h. The UK Parliamentary Office for Science and Technology POSTNote can be accessed at http://www.parliament.uk/briefing-papers/POST-PN-431

Ev i. The Chief Medical Officer for the UK and the Department for Health. A press release describing the decision reached and including the quotation used can be accessed at https://www.gov.uk/government/news/innovative-genetic-treatment-to-prevent-mitochondrial-disease