Institution: University of Bath

Unit of Assessment: A5 Biological Sciences

Title of case study: Research-led policy influence on Bioethics in genome editing and human reproduction

Period when the underpinning research was undertaken: 2010 - 2020

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Professor ACF (Tony) Perry	Professor, Head of Laboratory of Mammalian Molecular Embryology, previously Reader	April 2010 – present

Period when the claimed impact occurred: 2015 – 2020

Is this case study continued from a case study submitted in 2014? N

1. Summary of the impact

Professor Perry's work has informed the regulatory environment on human genome editing. Through his research and panel membership, it has directly influenced key recommendations by two bodies: the Human Fertilisation & Embryology Authority (HFEA; Expert Panel on Human Mitochondrial Replacement) and the Nuffield Council on Bioethics (Core Working Group on Human Genome Editing). As a direct result of the former, the HFEA established parameters enabling them to grant the first license authorising mitochondrial replacement therapy to prevent mitochondrial disease. The UK is the first country in the world to license prescriptive human genome modification.

2. Underpinning research

Advances in genome research present a significant opportunity for treating serious medical conditions, including mitochondrial disease and heritable conditions due to mutations in nuclear genomic DNA. However, in addition to technical challenges that must be appreciated and met, they present substantial ethical issues. This Case Study shows how University of Bath research in genome editing directly influenced key recommendations in these areas.

Professor Perry has a long track record of developing techniques for genome modification in living mammals. He is one of the few to have reported nuclear transfer (nt) cloning of more than one species (mice and pigs), and of cloning both from embryonic stem (ES) cells and to produce them (introducing the term 'ntES cell'). Research techniques used in Professor Perry's work (notably intracytoplasmic sperm injection, ICSI) are closely related to methods used in human clinical procedures such as in vitro fertilisation (IVF).

The Perry lab discovered the decades-long-sought cytostatic factor, Emi2 and reported its mechanisms. It was the first to report gamete miRNA and protein profiles and demonstrate that zinc ions are pivotal to meiotic arrest, working through Emi2. This transformative work is represented in textbooks (e.g. 'Principles of Development', Wolpert *et al*., 2015).

Research germane to this Impact Case Study includes (in 2011) the generation of England's first adult vertebrate cloned from an adult [1]. In 2014, the lab demonstrated that the intracytoplasmic sperm injection (ICSI) procedure used in human IVF could effectively be used for genome editing. This was a pioneering UK technical contribution to mammalian genome editing [2] and the lab subsequently integrated it with genetic code expansion to achieve inducible editing [3]. In

2016, the group overturned the two-centuries-old dogma that successful fertilisation must involve an egg, by 'fertilising' an embryo to produce offspring [4]. In 2019, the Perry lab challenged the role of sperm RNA in fertilisation [5] and using intracellular nanodevices to track force changes in one-cell embryos, reported a trans-disciplinary 'first' to understanding cellular mechanical properties [6]. This open and integrative approach has thus provided the UK with a major research stake in the new age of embryo manipulation and genome editing.

This has direct relevance to establishing key methodologies and protocols for interventions in human embryology. The fact that the genome editing developed by the Perry group harnesses the process of fertilisation itself placed him in an influential position to provide technical advice in this fast-moving field: policy must faithfully embrace latest research breakthroughs to respond to them effectively. This need is best met when those involved in advising on policy have hands-on expertise in the very latest technologies; Professor Perry's research outputs in this area (adopting the CRISPR technique [2] and developing new approaches that were specifically noted in the Nuffield Council Bioethics working group remit – "*explore the ethical issues raised by novel genome editing techniques, such as the CRISPR-Cas9 system*") placed him in the ideal position to contribute to policy as outlined below.

3. References to the research

[1] VerMilyea, MD, Maneck, M, Yoshida, N, Blochberger, I, Suzuki, E, Suzuki, T, Spang, R, Klein, CA & Perry, ACF 2011, 'Transcriptome asymmetry within mouse zygotes but not between early embryonic sister blastomeres', *EMBO Journal*, vol. 30, no. 9, pp. 1841-1851. https://doi.org/10.1038/emboj.2011.92

[2] Suzuki, T, Asami, M & Perry, ACF 2014, 'Asymmetric parental genome engineering by Cas9 during mouse meiotic exit', *Scientific Reports*, vol. 4, 7621. https://doi.org/10.1038/srep07621 S

[3] Suzuki, T, Asami, M, Patel, SG, Luk, LYP, Tsai, Y-H & Perry, A 2018, 'Switchable genome editing *via* genetic code expansion', *Scientific Reports*, vol. 8, no. 1, 10051, pp. 1-12. https://doi.org/10.1038/s41598-018-28178-3

[4] Suzuki, T, Asami, M, Hoffmann, M, Lu, X, Gužvić, M, Klein, CA & Perry, ACF 2016, 'Mice produced by mitotic reprogramming of sperm injected into haploid parthenogenotes', *Nature Communications*, vol. 7, 12676, pp. 1-15. https://doi.org/10.1038/ncomms12676

[5] Zhou , D, Suzuki, T, Asami, M & Perry, A 2019, 'Caput epididymidal mouse sperm support full development.', *Developmental Cell*, vol. 50, no. 1, pp. 5-6. https://doi.org/10.1016/j.devcel.2019.05.012

[6] Duch, M, Torras, N, Asami, M, Suzuki, T, Arjona, M, Gómez-Martínez, R, VerMilyea, M, Castilla, R, Plaza, JA & Perry, A 2020, 'Tracking intracellular forces and mechanical property changes in mouse one-cell embryo development', *Nature Materials*, vol. 19, no. 10, pp. 1114-1123. https://doi.org/10.1038/s41563-020-0685-9

4. Details of the impact

Key influence on policy and public understanding

Activities leading up to the delivered impact resulted directly from the influential published work of Professor Perry in molecular embryology. He was appointed to the core working group on genome editing at the Nuffield Council on Bioethics [A], an independent body advising policy makers internationally and stimulating debate in bioethics. The working group recommendations were presented in the form of a detailed Platform Report published in October 2018. The Report prompted broad international debate due to its content and the ensuing recommendations of the Nuffield Council. Professor Perry was also appointed to the HFEA Expert Panel (of six) on mitochondrial replacement [A], whose work has delivered substantive policy and regulatory impacts and whose influential activities are detailed below in the context of the delivered Impact.

Human Fertilisation and Embryology Authority (HFEA) Expert Panel on Mitochondrial Donation

As background, mitochondrial diseases result from mitochondrial dysfunction; they manifest as a wide range of serious symptoms, including seizures, strokes, severe developmental delays, inability to walk, talk, see, digest food and many other complications. Heritable mitochondrial disease is most severe in children and estimated to affect 1 in approximately 4,000 people. As mitochondrial disease is presently incurable, there is a focus on reducing the likelihood of mitochondrial disease inheritance.

With Parliamentary legislation permitting mitochondrial replacement therapy, implementation awaited the key licensing decisions to allow these procedures to be undertaken. In order for clinics to offer treatment, they must first be granted a specific license to do so by the relevant regulatory instrument of the Human Fertilisation and Embryology Act; the statutory licensing authority is the HFEA. To reach a decision as to whether such licenses should be granted, the HFEA convened the Expert Panel [B] to consider the efficacy of therapeutic mitochondrial transfer and provide recommendations on this important issue.

Having considered published and unpublished international evidence, the Panel produced a detailed report that has been adopted by the HFEA in its decision to license individual applications for legally approved mitochondrial replacement therapy (MRT). This specifically delivers impact on "decisions by a regulatory authority informed by research".

The Panel presented its findings to the HFEA in 2016 [C]. Two techniques for mitochondrial donation had been approved by Parliament in 2015 [D]: maternal spindle transfer (MST, in which the nuclear genetic material is removed from the parent's eggs and transferred into donated eggs whose nuclear genetic material had been removed); and pronuclear transfer (PNT, eggs are fertilised in the lab to create embryos, from which the nuclear genetic material is then transferred into embryos created using donated eggs). The link of this to Professor Perry's expertise and research work is summarised in general terms in a national newspaper article, The Observer, in 2015 [E].

Although in permitting MRT in the clinic, the UK government acknowledged that mitochondrial and nuclear genomes are distinct, the link between Professor Perry's research in germ-line therapy and mitochondrial replacement is clear. "*Perry's work [in Reference [3] above] added a unique flourish. He did the editing not in a one-cell mouse embryo – which is how most animal germ-line editing by Crispr has been done to date – but earlier, during the process of fertilisation, by injecting the Crispr components and the mouse sperm into the mouse egg at the same time. It is the same technique – intracytoplasmic sperm injection (ICSI) – widely used in IVF. And it worked*" [E]. Professor Perry had also published on mitochondrial transfer in the mouse.

Within two weeks of the panel reporting in 2016, the HFEA made the decision that specialist IVF clinics could apply for permission to use mitochondrial donation for risk reduction treatments in certain cases where alternative treatments would be of little or no benefit to mothers at risk of passing mitochondrial disease onto their children [F].

These recommendations have been directly incorporated into HFEA guidelines [G]; in short, the report **directly influenced licensing by the HFEA of MRT and the conditions under which it did so, making the UK the first country in the world to regulate mitochondrial donation.** The leading role the UK has established in being the first to licence such procedures has set a **benchmark for genome modification internationally.** The keen interest in the potential adoption of similar regulated approaches in other countries world-wide also focuses on the key role of HFEA and how it is able to respond to such expert advice.

More widely, Professor Perry's body of research in this area enables him to act as an expert advocate, communicating the serious underlying issues that the HFEA and panels seek to address. This fosters informed debate in this important and high profile area [E, H-J]. Professor Perry has addressed the House of Lords and global audiences of over 1,000,000 to 100,000,000

via television (e.g. CNN, Fox), presenting at TEDx, and in the UK *via* television (e.g. The Nine O'clock News, BBC1) and radio (e.g. Today, BBC R4).

5. Sources to corroborate the impact

[A] Letters of appointment to HFEA Expert Panel and Nuffield Bioethics Nuffield Council on Bioethics core working group on genome editing, 13 and 18 June 2015.

[B] HFEA Press Release appointing expert panel, 2016. https://www.hfea.gov.uk/about-us/news-and-press-releases/2016-news-and-press-releases/hfea-reconvenes-independent-mitochondrial-expert-panel/

[C] HFEA Press Release announcing expert panel recommendations, 2016. https://www.hfea.gov.uk/about-us/news-and-press-releases/2016-news-and-press-releases/uks-independent-expert-panel-recommends-cautious-adoption-of-mitochondrial-donation-in-treatment/

[D] Article in The Guardian, 3 February 2015. https://www.theguardian.com/science/2015/feb/03/mps-vote-favour-three-person-embryo-law

[E] Article in The Observer, 10 May 2015. https://www.theguardian.com/science/2015/may/10/crispr-genome-editing-dna-upgrade-technology-genetic-disease

[F] HFEA Press Release announcing permission for use of mitochondrial donation, 2016. https://www.hfea.gov.uk/about-us/news-and-press-releases/2016-news-and-press-releases/hfea-permits-cautious-use-of-mitochondrial-donation-in-treatment-following-advice-from-scientific-experts/

[G] HFEA Code of Practice, October 2018. https://www.hfea.gov.uk/media/2565/hfea-draft-code-of-practice-9th-edition-consultation-version.pdf

Wider dissemination

[H] Progress Educational Trust Conference 2015, “From Three-Person IVF to Genome Editing: The Science and Ethics of Engineering the Embryo”. https://www.progress.org.uk/conference2015

[I] PHG Foundation Article, “Call for debate on human genome editing”, January 2015. [PHG Foundation (Cambridge): Web page Archived, available on file]

[J] BBC News Website Article, January 2015. https://www.bbc.co.uk/news/health-30742774 (Covers Perry’s work, refers to source [C])