Mitochondria Replacement: Ethics, First Human Trials, and Treatment for Genetic Disease

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Disclosure Statement

- *I was chair of the Institute of Medicine (now National Academy of Medicine) consensus committee on the "Ethical and Social Policy Considerations of Novel Techniques for Prevention of Maternal Transmission of Mitochondrial DNA Diseases"*

Why pursue MRT?

- Parental desire for offspring sharing a nuclear DNA connection with both parents is widely held (but not universal)
- Not all goals of prospective parents are met by present alternatives
  - Unassisted sexual reproduction, PGD
  - Oocyte and embryo donation, adoption, childlessness

Mitochondrial Biology and Genetics

Mitochondria: subcellular, cytoplasmic organelles important for cellular energy production

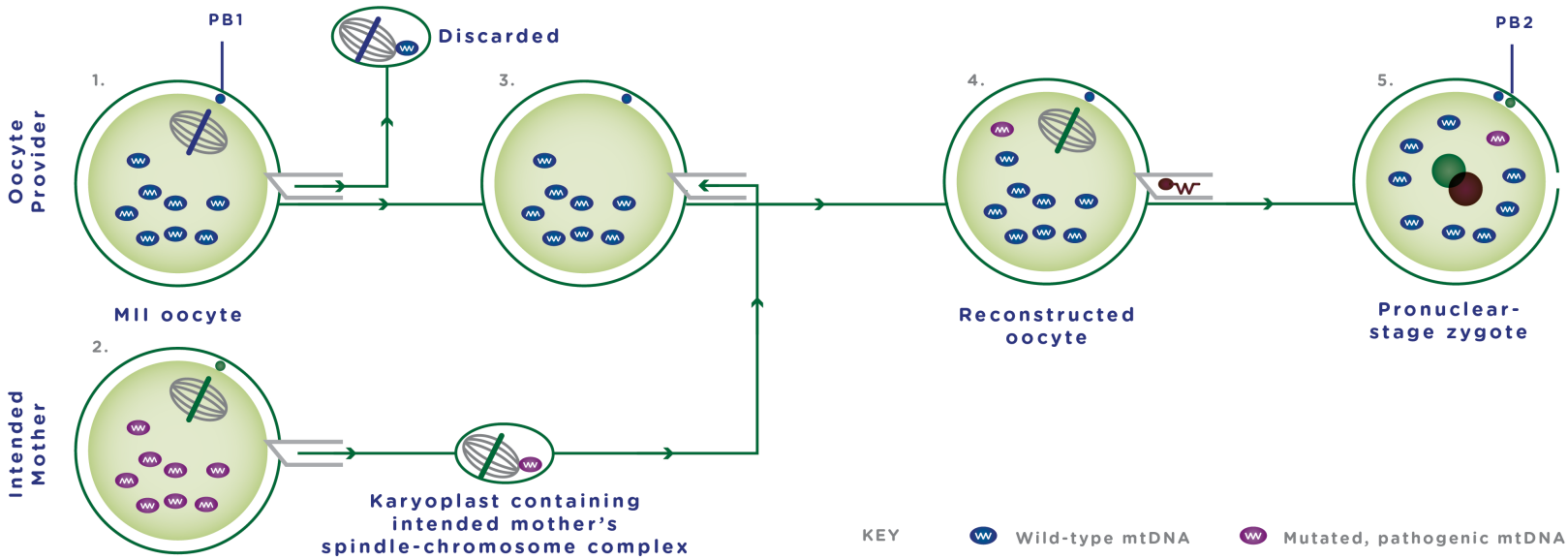
- Also regulate other cellular functions, such as: calcium homeostasis, apoptosis, metabolism

Mitochondria contain own extracellular genome (mtDNA)

• Circular chromosomes	nDNA: linear
• 37 coding genes	nDNA: 20-30,000
• 100-10,000 copies per cell	nDNA: 2 of each chromosome
• Maternal inheritance	nDNA: biparental

- Can exhibit heteroplasmy (state in which a cell, tissue, or individual contains more than one type of mtDNA genotype)

MRT: Maternal Spindle Transfer



SOURCE: Modified figure based on those appearing originally in: Richardson, J., L. Irving, L. A. Hyslop, M. Choudhary, A. Murdoch, D. M. Turnbull, and M. Herbert. 2015. Concise reviews: Assisted reproductive technologies to prevent transmission of mitochondrial DNA disease. Stem Cells 33(3):639-645. License information available at: http://creativecommons.org/licenses/by/4.0/

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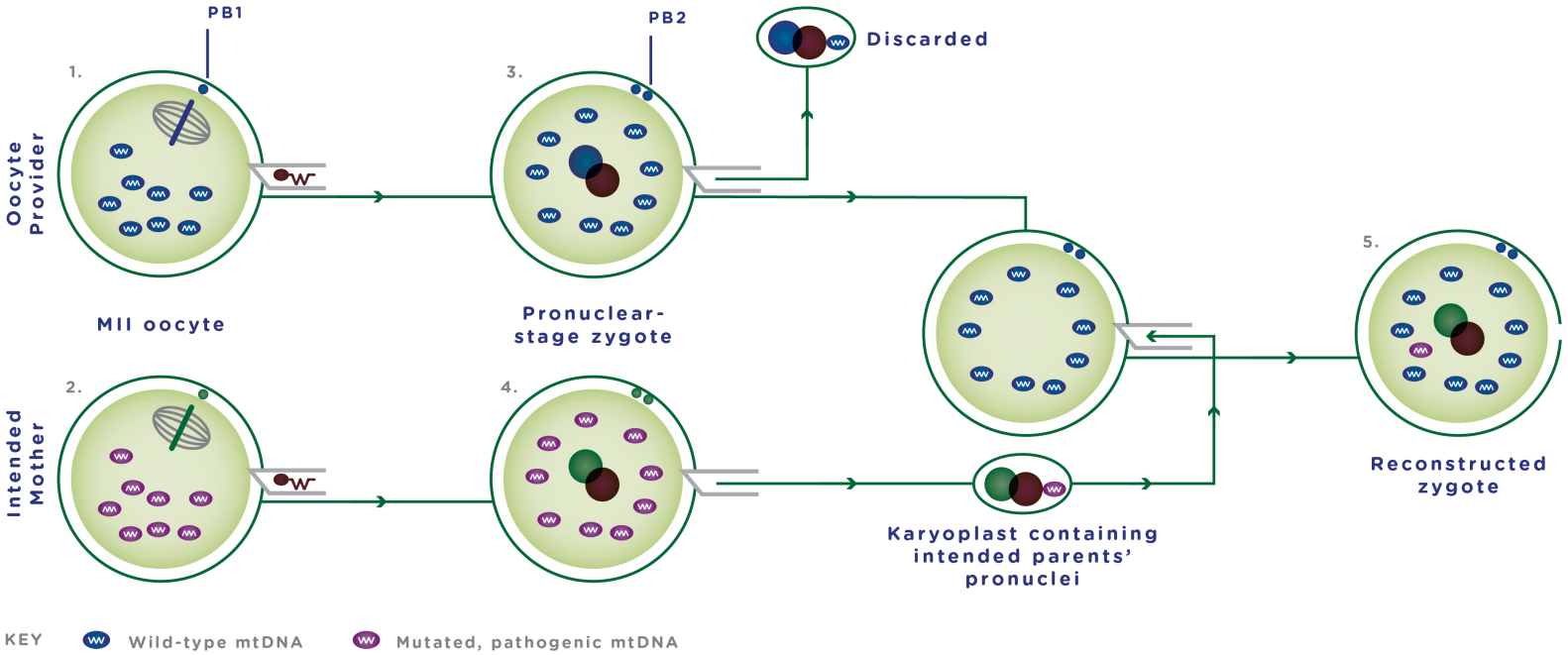
MRT: Pronuclear Transfer



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Ethical Analysis

Identity, Kinship, and Ancestry

- Genetic contributions from two women of different maternal lineage would introduce complexities that might affect the child's experiences of identity, kinship, or ancestry
- A matter for reflection by families undertaking MRT and societal discussions
- The complexities alone are not sufficient to justify prohibiting initiating MRT clinical investigations

Ethical Analysis

Genetic modification of germ cells and the germline

- MRT results in genetic modification of germ cells
  - MRT producing female offspring would constitute heritable genetic modification (germline modification)
  - MRT producing male offspring would not constitute heritable genetic modification because the modifications would not be passed down

Ethical Analysis

Genetic modification of germ cells and the germline

- Some cite concerns about genetic modification of germ cells
  - Safety
  - Interference with nature/"playing God"
  - Eugenics/attitudes towards disability
  - Crossing the germline
- Concerns about human genetic modification or germline modification warrant significant caution and the imposition of restrictions rather than a blanket prohibition on MRT to prevent transmission of serious mtDNA disease

Ethical Analysis

Distinctions – modification of mtDNA vs nDNA

- Replacement of whole, intact, and naturally occurring mitochondrial genome
- Traits carried in nDNA are those that in the public understanding constitute the "core" of genetic relatedness
- While energetic "enhancement" to improve the function of mtDNA with regard to increased cell energy might hypothetically be possible through MRT, this appears to be far more speculative relative to modification of nDNA
- These distinctions do not imply that mtDNA is unimportant but that its modification is meaningfully different from that of nDNA

Ethical Analysis

Other Considerations

- Expanded applications:
  - Differences between mtDNA and nDNA, and the nature of the replacement techniques, help circumscribe applications and provide natural limits on the potential for misuse.
  - Regulations and guidelines are needed to limit the use of MRT to the prevention of transmission of serious, life-threatening mtDNA diseases and to prevent slippage into applications that raise other serious and unresolved ethical issues

Ethical Analysis

Conclusion

- Ethical, social, and policy issues can be avoided through limitations on the use of MRT or are blunted by the significant and important distinctions between genetic modification through MRT and modification of nDNA
- It is ethically permissible to conduct MRT clinical investigations
- Conditions and principles are needed

Initiating Human Clinical Investigations

Conditions for initial MRT clinical investigations:

- Initial safety is established; risks to all parties are minimized with consideration of minimizing risk to future children of highest priority
- Likelihood of efficacy is established by preclinical research
- Limited to women at risk of transmitting serious mtDNA disease; mutation's pathogenicity is undisputed; and disease is predicted to be severe
- Initially, to reduce the risk of adverse effects being realized by multiple generations, uterine transfer is limited to male embryos

Principles for a Cautious Approach

Regulators should ensure that design and conduct of all MRT clinical investigations adhere to the following:

- Health and well-being of any future children born as a result of MRT protocols have priority in the balancing of benefits and risks
- Study designs should be standardized to the extent possible to enable comparisons and pooling
- Data from research or clinical practices from wherever MRT is performed should be incorporated into regulators' analysis
- Clinical investigations should also collect long-term information regarding health, psychological, and social effects on children conceived as a result of MRT, including their perceptions about their identity, ancestry, and kinship

Informed Consent

- Need for special attention to communicating the novel aspects of MRT research to potential research participants including gamete providers, intended parents, and children conceived as a result of MRT (assent/consent for monitoring and follow-up)

Guiding Principles for Oversight

- Transparency
  - Timely public sharing of information
  - Encourage sponsors to commit to depositing protocols and de-identified results in public databases
- Public engagement – Exploration of stakeholder views including public meetings
- Partnership – Collaborate with other regulatory authorities
- Maximizing data quality – Enable cross-referencing and pooling of data
- Circumscribed use
- Long-term follow-up

New Scientist

DAILY NEWS 27 September 2016, updated 27 September 2016

By **Jessica Hamzelou**

It's a boy! A five-month-old boy is the first baby to be born using a new technique that incorporates DNA from three people, *New Scientist* can reveal. "This is great news and a huge deal," says Dusko Ilic at King's College London, who wasn't involved in the work. "It's revolutionary."

The controversial technique, which allows parents with rare genetic mutations to have healthy babies, has only been legally approved in the UK. But the birth of the child, whose Jordanian parents were treated by a US-based team in Mexico, should fast-forward progress around the world, say embryologists.

Neither method has been approved in the US, so Zhang went to Mexico instead, where he says "there are no rules". He is adamant that he made the right choice. "To save lives is the ethical thing to do," he says.

New Scientist

DAILY NEWS 10 October 2016

Exclusive: '3-parent' baby method

By Andy Coghlan

The first babies to be created using a "three-parent" method to overcome their parents' infertility are due to be born in early 2017. *New Scientist* has learned that two women in Ukraine are both more than 20 weeks pregnant with fetuses created using such a technique.

The babies would be the first born to women who had the procedure to treat infertility, rather than to prevent hereditary disease, but some have criticised this approach, calling for it to be banned until there is more evidence that the embryos it creates are healthy.

Reproduction

UK doctors select first women to have 'three-person babies'

Two women carrying mutations that cause rare genetic disease to undergo radical therapy

Ian Sample *Science editor*

@iansample

Thu 1 Feb 2018 13.48 EST

Doctors in Newcastle have been granted permission to create Britain's first "three-person babies" for two women who are at risk of passing on devastating and

The Human Fertilisation and Embryology Authority (HFEA) confirmed on Thursday that it had approved the procedures which will now be overseen by Mary Herbert, professor of reproductive biology, and her team at the Newcastle clinic.

The women will be the first in Britain to have so-called mitochondrial donation therapy, a radical IVF procedure that was made legal by parliamentary vote in 2015. The Newcastle centre was granted a licence to perform the treatment, also known as mitochondrial replacement therapy, in March last year.

While doctors at Newcastle Fertility Centre said they could not to talk about the cases, citing patient confidentiality, minutes from the HFEA's approval committee reveal that the two women carry mutations in a gene that causes a rare condition known as myoclonic epilepsy with ragged red fibres, or Merrf syndrome. No more details are given on the women because both wish to remain anonymous.

A baby in Greece was born with 3 parents after doctors used an experimental technique to make 'medical history'

Beatrice Christofaro Apr. 11, 2019, 8:58 AM