# Preventive mitochondrial replacement

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**Techniques used recently to clone a sheep generate chimeras with the genome of the donor cell and mainly the mitochondria of the acceptor egg. The use of the same techniques should allow a mother carrying a mitochondrial defect to bear a normal child with normal mitochondria.**

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The recent successful cloning of a sheep [1], and the consequent perception that the cloning of a person may be possible, has led to extensive discussion of the ethical issues involved. Benefits to humankind such as simplified drug development and the production of high milk producing herds have been arrayed against the potential horrors of cloning animals and humans. One potential application of cloning techniques has been overlooked in the public debate, however, namely the production of single-copy chimeras in which the nuclear genome is identical to that which would result from a normal pregnancy but the mitochondrial genome comes from an independent donor.

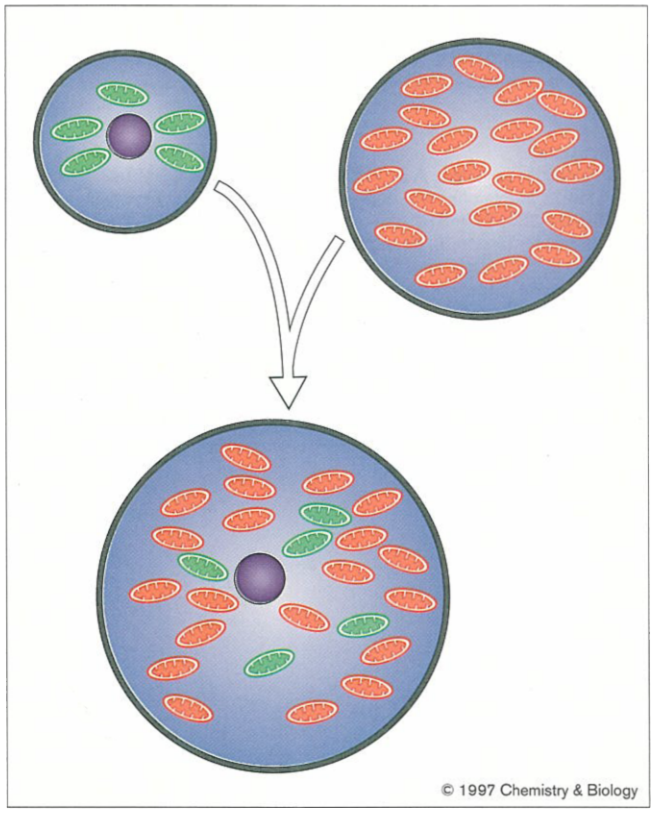
Mitochondria are intracellular organelles responsible for the synthesis of ATP, the major energy source for biochemistry. They have a small DNA genome that encodes proteins essential for mitochondrial function. There are a substantial number of rare diseases that are caused by mutations in the mitochondrial genome (Table 1). According to the United Mitochondrial Disease Foundation, about one person in 10 000 carries a mitochondrial mutation (see The United Mitochondrial Disease Foundation internet site, http://biochemgen.ucsd.edu/UMDF/AboutMitoDisease.htm). The mitochondria of a fertilized egg are derived from the mother, with no paternal contribution. Consequently, mitochondrial diseases are transmitted maternally. The following steps might enable a mother carrying a clinically significant mitochondrial mutation to produce a normal child (for related ideas see [2,3]). First, initiate a normal pregnancy. Second, harvest embryonic cells. Third, fuse one of the embryonic cells as donor to an acceptor egg with normal mitochondria from which the nucleus has been

**Table 1**

**Some inherited diseases of the human mitochondrial genome.**

| Disease | Symptoms |
|---|---|
| Cytochrome *c* oxidase deficiency | Loss of appetite, muscle weakness, lactic acidosis |
| Hypertrophic cardiomyopathy | Shortness of breath, chest pain, fainting episodes |
| Kearns–Sayre syndrome | Eye-movement disorders, heart arrhythmias |
| Mitochondrial encephalomyopathy | Seizures, stroke-like episodes, lactic acidosis |
| Myoclonic epilepsy | Seizures, dementia, hearing loss, loss of balance |
| Pyruvate dehydrogenase deficiency | Lactic acidosis, central nervous system degeneration |

**Figure 1**




Transfer of nucleus (purple) from donor cell together with a small number of abnormal mitochondria (green) into an enucleated egg which has many normal mitochondria (red). The nucleus is removed from the egg using a micropipette, and fusion of the donor cell to the egg is induced by electrical pulses [1].

removed (Fig. 1), using techniques similar to those established for sheep, if this can be done in humans. Finally, implant the egg in the original mother.

This sequence of procedures should result in an individual who would differ from the individual who would have arisen from a normal pregnancy only in having a mitochondrial pool containing both donor and acceptor mitochondria. The choice of donor cell type should make it possible to obtain a chimera in which the majority of the mitochondria come from the egg.

Mitochondrial replacement might fail for a number of reasons, for example if mutant mitochondria replace normal mitochondria during development. Furthermore, *in vitro* fertilization methods might make it unnecessary to harvest embryonic cells, or make it possible to transplant nuclei between unfertilized oocytes [4] and thus to eliminate completely the need for cloning procedures. In view of these uncertainties, and because the number of people who would be helped is small, mitochondrial replacement is not a justification for the extension of cloning to humans. Nevertheless, mitochondrial replacement is a topic that could be considered in the ongoing debate on the ethics of cloning.

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