NYSCF
The New York
Stem Cell Foundation
Research Institute

Mitochondrial Replacement Therapy FAQs

What are mitochondrial diseases? How do you get them?

Mitochondria are small structures found in our cells, which generate the cellular energy used to power every part of our body. Known as the cell's "powerhouse," you can think of them as tiny, but very important, engines that are in each of your body's cells.

Mitochondria contain their own DNA, which controls mitochondrial function and energy production. The mitochondrial DNA makes up less than 0.0005% of all our DNA, and is completely separate from our 'nuclear DNA,' which makes us who we are and determines physical traits and personality.

Importantly, this mitochondrial DNA comes only from the mother, not the father. So, if there are mutations to a woman's mitochondria, she is at risk of both developing a mitochondrial disease and transmitting this kind of disease to her children.

Approximately 1 in 5,000-10,000 children are born each year with mitochondrial disease.

These can be devastating diseases, with symptoms often arising in childhood. Although there are various kinds of mitochondrial diseases, symptoms can include stunted development, neurological disorders, heart disorders and stomach and digestive problems, among others, and can result in childhood death. There are no cures to these diseases—only symptom management.

There are three ways of getting a mitochondrial disease: inheriting mutant mitochondria from your mother, and inheriting a mutation from both parents within your nuclear DNA that affects mitochondria causing mitochondrial disease. The novel techniques in question can prevent the first type of mitochondrial disease inheritance.

Can you prevent these diseases?

No, with current treatments, doctors cannot prevent transmission of these diseases. However, the methods up for approval in the UK that were developed by New York Stem Cell Foundation (NYSCF) scientists and others should (and will) prevent the transmission of these diseases from mother to child.

A woman with a mitochondrial disease or a woman who has had a previous child with one of these disorders has three options:

- She could elect to have no further children.
- She could undergo in-vitro fertilization (or IVF) with a donor's egg, but the child will not be genetically related to her.

- She could undergo IVF, and clinicians can screen her embryos and select the one with the least number of mitochondrial defects. This last option reduces—but does NOT—eliminate the risk that her child will develop mitochondria disease. Such genetic screening can eliminate nuclear mutations, but cannot eliminate mutant mitochondrial DNA.

Can you describe the techniques?

Termed 'mitochondrial donation' in the UK and often called 'mitochondrial replacement therapy' or MRT in the US, the two techniques that could be used to prevent the transmission of mitochondrial diseases are maternal spindle transfer and pronuclear transfer.

In maternal spindle transfer, the nuclear DNA of a donor egg is removed, leaving the healthy mitochondria, and replaced with the nuclear DNA from an egg from a woman with mitochondrial disease. This cell is then fertilized and implanted into the mother in the same way IVF is currently carried out.

Pronuclear transfer involves a similar procedure as maternal spindle transfer, however, the egg is fertilized first, then the fertilized nuclear DNA, or pronucleus, is transferred to a healthy donor egg (which has had it's nuclear DNA removed, leaving healthy mitochondria). This egg is then implanted in the mother in the same way as in maternal spindle transfer. Research on both techniques is ongoing, and potential advantages of one technique over the other are being considered.

For patients with mitochondrial diseases, this means that these two methods could prevent the transmission of faulty mitochondrial genes to children.

Why is this significant?

Mitochondrial replacement techniques would eliminate maternal transmission of mitochondrial disease.

The results are significant because they may help to prevent the inheritance of mitochondrial diseases. Approximately 1 in 5,000-10,000 children are born with mitochondrial diseases due to the presence of mutant mitochondrial DNA in a cell. Researchers estimate that over 12,000 women in the US could benefit from these techniques – almost 800 births a year (*NEJM*).

NYSCF and Columbia University Medical Center scientists and clinicians have shown that it is possible to transfer the nuclear genome from one egg to another egg, resulting in a complete exchange of the mitochondrial DNA. This technique would allow a woman with a family history of mitochondrial diseases to ensure her children would not be affected.

How long until we see this in the clinic?

Approval is currently under debate in the UK, and is scheduled for debate by Parliament on February 3rd, 2015. Upon approval by the parliament, HFEA will be able to grant a license to specific clinics interested in evaluating this treatment. In the US, research institutions will have to apply for approval from the Food and Drug Administration. Then, approval depends on the progress of a public discourse,

the establishment of guidelines, and regulatory approvals before any US entities will be able to move forward with either of the two techniques in the clinic.

Does this therapy stop the family history of mitochondrial diseases?

Yes; if a woman were to undergo this therapy, it would eliminate the mutant mitochondrial DNA from future generations.

In a paper published in *Nature* in 2011, NYSCF Research Institute scientists showed that the exchange of the mitochondrial genotype can be complete (specifically, the mitochondrial genotype of the egg from which the nuclear genome is taken is eliminated) and stable under various scenarios that have the potential to alter the mitochondrial genotype. The scientists cultured stem cells with the swapped mitochondrial genotype for more than a year, and then turned them into the cell types that can be affected by mitochondrial disease, such as neurons, beta cells, cardiomyocytes (or, heart muscle cells). The scientists looked at the grown cultures, expanded from single cells, and reprogrammed these cells, subjecting the mitochondrial DNA to a bottleneck similar to the one during oocyte development. The scientists never observed the re-emergence of the 'old' mitochondrial genotype. They also observed that mitochondrial functions were normal.

What are your next steps to accelerate this work to the clinic?

The number of pre-clinical studies in human cells is currently small. Additional studies are being conducted to further assess the safety and efficacy of mitochondrial replacement. Next steps already underway include the generation of larger numbers of transferred oocytes and the establishment of standardized and detailed protocols.

What has been done in the US lately?

There was an FDA Cellular, Tissue and Gene Therapies Advisory Committee hearing last February 25-26th on the scientific merits of mitochondrial replacement techniques. This committee has no decision making power, however, they advise the FDA and recommended the agency wait for further information from preclinical studies before approving mitochondrial replacement therapy in human trials in the US. The decision in the UK will likely inform discussion on proceeding in the US.

What is the status of mitochondrial donation in the UK?

The UK Human Fertilization and Embryology Authority (HFEA) convened an Expert Scientific Review panel specifically to scrutinize the safety of these procedures. Through three separate reviews, the panel found no evidence that these techniques were unsafe for clinical use. There were also public hearings in the UK on mitochondrial donation to assess the public opinion towards such therapy. With overwhelming public support, Parliament has scheduled a hearing on February 3rd, 2015 on allowing a track for use of the therapy in select approved situations. If the regulations are passed, specialist clinics will have to obtain a license from the HFEA to use the techniques. Further, these techniques will only be available to a specific group of women with mitochondrial mutations and doctors will assess and discuss in detail the different reproductive options for each patient before use.