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Is there treatment for Leber Hereditary Optic Neuropathy?

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Abstract

Purpose of review—To discuss recent advances in potential treatments for Leber hereditary optic neuropathy (LHON), a typically visually devastating hereditary optic neuropathy caused by mutations in the mitochondrial genome.

Recent findings—Idebenone has been proposed as a means of bypassing defective complex I activity and a free radical scavenger to prevent oxidative damage. EPI-743 may have more potency than idebenone, but no clinical trials have been performed. Gene therapy techniques have advanced significantly, including allotopic expression and nuclear transfer. Successful rescue of animal models of LHON with both of these therapies has been demonstrated. Introduction of exogenous DNA into the mitochondrial genome with mitochondrial targeting of viral vectors is another promising technique.

Summary—There are currently no proven treatments for Leber hereditary optic neuropathy. However, there are many promising novel treatment modalities that are currently being evaluated, with several clinical trials underway or in the planning stages. Supportive measures and genetic counseling remain of great importance for these patients.

Keywords

Leber hereditary optic neuropathy; optic neuropathy treatment; gene therapy; mitochondria; idebenone; allotopic transfer

Introduction

Leber hereditary optic neuropathy is an inherited bilateral isolated optic neuropathy caused by mutations in the mitochondrial DNA (mtDNA).¹⁻³ Three primary point mutations account for about 90% of LHON cases (m.11778G>A, m.3460G>A, m.14484T>C), with the

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Disclosure: Idebenone, EPI-743, and gene therapy are currently not FDA approved for the treatment of Leber hereditary optic neuropathy.

mutation at the 11778 locus being the most common and having the worst visual prognosis, and the 14484 locus associated with the best visual prognosis.¹⁻³ These mutations lead to abnormalities in the structure of proteins involved in the mitochondrial respiratory chain within complex I. Altered function of these proteins likely causes some decrease in ATP synthesis, but most importantly an increase in free radical production and oxidative damage.

Classically LHON presents with bilateral vision loss, which is painless, central, and symmetric.¹⁻³ Visual acuities are typically 20/200 or worse bilaterally.¹⁻³ The time between involvement of each eye is typically 2-4 months, and second eye involvement occurs in at least 97% of cases within one year. Vision loss is usually permanent, although more than 50% of patients who harbor the 14484 mutation will have some spontaneous improvement. Younger patients have a higher chance of vision recovery, especially those younger than 10 years of age.^{1,3,4} The optic nerve becomes pale, most significantly temporally, as the papillomacular bundle is preferentially affected.

LHON provides a naturally occurring “laboratory” for novel therapies and clinical trials given the bilateral sequential nature of the disease. In about 50% of cases, this window of opportunity is clinically recognized, allowing for potential prevention of vision loss in the second eye. Also, unique to this piece of central nervous system tissue, therapies can be delivered directly to the tissue involved, in this case to the retinal ganglion cells via intravitreal injection or topical therapy. Treatment effect can be monitored through visual function measures, and objectively measured with retinal ganglion cell layer morphometry using optical coherence tomography. The eye is an immune-privileged site, making it ideal for gene therapy trials with viral vectors. A near 100% rate of involvement of the second eye makes prevention of bilateral occurrence a clearly measurable outcome for treatment trials.⁵

Treatments

General treatments for mitochondrial disease

Various formulations for so-called “mitochondrial cocktails” have been used to treat mitochondrial diseases, including LHON. Coenzyme Q₁₀, L-carnitine, creatine, lipoic acid, dimethylglycine, cysteine, succinate, dichloroacetate, vitamin K₁, vitamin K₃, vitamin C, vitamin B₁, vitamin B₂, and vitamin E have all been suggested as treatment for LHON, but there is currently insufficient evidence to support their use.^{1,3,6}

Co-enzyme Q₁₀ is an electron shuttle between complex I and II of the transport chain in the mitochondrial membrane. Coenzyme Q₁₀ deficiency leads to mitochondrial encephalomyopathy due to interruption of oxidative phosphorylation. Treatment with coenzyme Q₁₀ is beneficial in this particular disease. It has been used in other mitochondrial diseases, including LHON, without clear benefit.^{1,3,6}

Idebenone

Idebenone is a short-chain benzoquinone related to Coenzyme-Q₁₀ which is capable of preventing reactive oxidative species from causing oxidative damage to cell membranes and mitochondria, and also prevents lipid peroxidation. Idebenone may facilitate bypassing Complex I and electron transport directly to Complex III.^{7,8}

An in vitro study of retinal ganglion cells deficient in Complex I demonstrated a protective effect of idebenone against cell death.⁹ Idebenone was also found to lead to prevention of retinal ganglion cell death, and recovery of vision, in mice treated with rotenone (a complex I inhibitor) as a model of LHON.⁹

Following several isolated case reports of idebenone leading to recovery of vision in patients with LHON, Mashima et al. evaluated treatment of LHON patients with idebenone combined with Vitamin C and Vitamin B₂, and found no differences in visual recovery, but proposed that recovery was more rapid when it occurred.¹⁰ A randomized, placebo-controlled, double-blind study of idebenone for patients with LHON (the Rescue of Hereditary Optic Disease Outpatient Study, RHODOS) evaluated patients who received 900mg/day of idebenone.¹¹ Although the trial failed to meet the primary outcome, subgroup analysis suggested that patients who had discordant visual acuities at the beginning of the trial (and therefore likely in the early stages of LHON) had better final visual acuities than patients who had more similar visual acuities in the two eyes at enrollment.¹¹

Dyschromatopsia is a common feature of LHON. Rudolph et al. evaluated the effects on idebenone on color vision in the RHODUS cohort, and found that patients treated with idebenone experienced an improvement in tritan color vision throughout the study, and lost less protan color vision at week 12, but this was not statistically significant at week 24.¹²

Long-term follow-up evaluation of patients enrolled in the RHODOS study was also performed in a single follow-up visit for observational purposes.¹³ The results revealed that the effects noted at the end of the RHODOS study persisted beyond the RHODUS trial time parameters, and it was reiterated that early treatment to preserve retinal ganglion cells may lead to the greatest benefit to the patient.¹³

Carelli et al. retrospectively evaluated the visual outcomes of 44 LHON patients who had been treated with idebenone within one year of developing vision loss in comparison to those who had not. They found that patients who harbored the 11778/ND4 mutation had a higher rate of visual recovery following treatment with idebenone.¹⁴ These patients with the 11778/ND4 mutation were more likely to experience vision recovery when treated with idebenone earlier in their disease course following initial vision loss. Patients with the 14484/ND6 mutation had a higher rate of spontaneous recovery regardless of treatment, as expected. Although the study was retrospective and non-randomized, with varying dosages of idebenone used, the authors concluded that idebenone may be an effective treatment for LHON.¹⁴ However, there was no prevention of second eye involvement in the six patients who were treated after involvement of the first eye, and final vision in the second eye was no different than that of the first eye.⁵

EPI-743

EPI-743 is a para-benzoquinone which replenishes glutathione stores and purportedly has much higher antioxidant activity in comparison to idebenone.^{15,16} The drug was given to five LHON patients with recent vision loss. Meaningful improvement was objectively achieved by only two patients: one man who harbored the 11778 mutation, and one who was a child with the 14484 mutation who was already predisposed to recovery.¹⁷ One case report

described two siblings with LHON due to the 14484/ND6 mutation, one of whom received EPI-743, and one who did not. This report acknowledged that these siblings were predisposed to recovery of vision because they harbored the 14484 mutation, however the younger sibling who received EPI-743 demonstrated rapid recovery of vision after administration of the drug, while the older sibling who did not receive the drug did not recover within the timeframe of followup.¹⁸ EPI-743 and idebenone are also being studied for their usefulness in mitochondrial diseases other than LHON. An open label study of EPI-743 used for Leigh's disease demonstrated neurologic improvement in all patients given the drug, and a randomized placebo-controlled trial was recommended to further evaluate the efficacy of this drug.¹⁹

Stem cell therapy

The availability of unproven therapies in areas of the world with less regulation and oversight of medical therapy, combined with the relative ease of international travel, have made the possibility of receiving stem cell infusions for any disease a reality. One case report described a patient with LHON who (purportedly) received umbilical stem cell infusions, both intrathecally and intravenously, with no improvement in vision, and no prevention of the development of optic atrophy.²⁰ There is currently no evidence that therapy with stem cells improves outcomes in LHON.

Gene therapy

Currently the most exciting potential means of treating LHON are within the field of gene therapy. LHON's unique characteristics as a mitochondrial disease that primarily affects the eye, with sequential involvement of the second eye, provides a "window of opportunity" for treatment and makes the disorder particularly suitable as an in vivo "laboratory." There are several forms of gene therapy which are being evaluated as possible treatments for LHON, at various stages of testing.

Exogenous DNA may be inserted into the nuclear DNA of a cell through viral vectors, such as recombinant adenovirus-associated virus (AAV) type 2. These vectors can be directly inserted into the eye, as has been successfully performed in clinical trials of Leber's congenital amaurosis due to mutations in the nuclear gene RPE65.²¹ As opposed to the nuclear genetic alteration in Leber's congenital amaurosis, the underlying problem in LHON lies in the mitochondrial genome. In order to circumvent the difficulties of inserting DNA into the mitochondrial genome, allotopic rescue has been employed. In this therapy, new genetic material is incorporated into the nuclear DNA, allowing for protein expression. Proteins encoded by this inserted genetic material can be targeted to translocate to the mitochondria. [Figure 1] This technique was successfully employed in cybrid cell lines, replacing the ND4 protein that was affected by the LHON 11778 mutation.^{22,23} Rescue of a mutant mouse model of LHON by this AAV vector containing wildtype allotopic *ND4* was successful, with preserved vision, restoration of ATP synthesis, and prevention of loss of retinal ganglion cells and optic nerve axons.²⁴ Similarly, in a rat model of LHON, Cwerman-Thibault et al. demonstrated the safety and efficacy of allotopic expression of wildtype human ND4 introduced by a recombinant AAV2/2 vector containing *ND4*, providing further evidence that gene therapy through allotopic expression in humans may be

possible for LHON.²⁵ Evaluation of the safety of injecting the viral vector in primates has demonstrated no serious adverse reactions.²⁴

As a result of the development of these novel gene therapy techniques, two human LHON gene therapy trials are currently enrolling patients, mostly to initially obtain human safety data.²⁶ A natural history observational study was performed evaluating patients with the 11778 mutation to determine what the course of visual signs and symptoms, and what were the structural outcomes.²⁷ Data from this study led the authors to decide that the primary outcome for a gene therapy trial should be visual acuity, with a 15-letter ETDRS improvement. Secondary outcomes could include retinal nerve fiber layer thickness, visual fields, and pattern electroretinograms.

As an alternative to using *ND4* in viral vectors, *ND11*, a yeast nuclear gene which encodes a complex I equivalent, has been used in murine and rat models demonstrating efficacy in protection from a rotenone induced model of LHON.^{28,29} The proposed advantage of using this gene over *ND4* is that this yeast gene would treat all mutations associated with complex I disease by replacing the entire complex I, not just the affected *ND4* subunit when replacing the *ND4* with the 11778 mutation with wildtype *ND4*.

Direct delivery and incorporation of genetic material within the mitochondria proves more difficult than allotopic expression, in part due to the double membrane of the mitochondria and separate system for gene expression. However, successful incorporation of human wild type mtDNA into mitochondria of cybrid LHON and Leigh syndrome cells was performed by complexing it with recombinant mitochondrial transcription factor A protein.³⁰ [Figure 2] Mitochondrial respiration and gene expression were found to be increased in these cells.³⁰ In 2012, Yu et al. described successful delivery and expression of wild-type *ND4* in mitochondria of a cybrid cell line that had been targeted for the mitochondria by fusing a targeting sequence to the AAV capsid.³¹ This was successfully performed in a murine model of LHON as well and demonstrated efficacy in preventing optic atrophy and vision loss in these mice.³¹ Next generation sequencing found no adverse recombination of the human *ND4* within the mitochondrial genome of the transfected mitochondria, indicating that this particular therapy is likely to be safe in patients with LHON.³² This vector was evaluated for toxicity and shows promise as another method to be used for a future gene therapy trial.³³

In gene shifting, mutant mtDNA is selectively destroyed, leaving only the non-mutant mtDNA in heteroplasmic mitochondrial diseases. [Figure 3] As described in Reddy et al, targeted endonucleases against particular mitochondrial disease haplotypes, including LHON and dystonia, led to elimination of the mitochondrial haplotype in oocytes and embryos, leaving only mitochondria with the selected haplotype, and resulted in phenotypically normal animals.³⁴ Offspring of the grown adults of oocytes that underwent mitochondrial selection were viable and demonstrated persistence of mitochondrial haplotype selection.³⁴ However, since most patients with LHON are homoplasmic, ¹⁻³ gene shifting maneuvers would likely not be beneficial for the majority of LHON patients.

Nuclear transfer, spindle-chromosomal complex transfer, or spindle transfer are forms of gene therapy treatment for women who wish to have offspring without mitochondrial

diseases. One technique removes the pronucleus of a fertilized zygote and places it into a donor zygote that has also had its nucleus removed.³⁵ Another technique removes the isolated metaphase II spindle of the maternal oocyte and places it into a donor oocyte that has had its nucleus removed.³⁶ The result is a zygote with normal maternal and paternal nuclear DNA contributions, but with donor cytoplasmic contents, including the mitochondria. [Figure 4] These techniques have been demonstrated to be feasible in primates and human oocytes, although some of the human oocytes displayed abnormal fertilization.^{36,37}

Genetic counseling and support

In all inherited diseases, genetic counseling, while not a treatment itself, is an essential component of the disease discussion with the patient to inform them of the risk of disease development in their children and relatives. Nearly all patients with LHON are homoplasmic, with all mitochondria expressing the pathogenic mitochondrial DNA. In mitochondrial disorders, men who are carriers of a mutation can be reassured that their offspring will not harbor the mutation. Children of a woman with LHON will all carry the mutation. However LHON has incomplete penetrance. Men who carry a pathogenic mutation have up to a 50% risk of developing LHON, while women have about a 10% risk.³

Patients with LHON have significantly decreased vision-related quality of life.³⁸ A referral to a low vision specialist may improve patients' quality of life through the prescription of low vision aids and facilitating techniques for reading and mobility.³⁹ Avoidance of tobacco use and heavy alcohol use should be encouraged in patients and their at-risk maternal relatives.^{40,41}

Conclusions

Leber hereditary optic neuropathy is an inherited mitochondrial disease with devastating visual consequences for those affected. Current treatment options are limited to supportive measures and therapies with questionable benefits. Idebenone can be considered for the patient early in the course of the disease. However, there are many potential therapeutic options that are currently being studied which may prove to be beneficial in the treatment or prevention of LHON.

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Key Points

1. Leber hereditary optic neuropathy currently has no proven treatment.
2. Symptomatic treatment and genetic counseling are important in the management of patients with Leber hereditary optic neuropathy.
3. Idebenone and EPI-743 may prove useful in the treatment of Leber hereditary optic neuropathy as free radical scavengers.
4. Multiple methods of gene therapy have been proposed to treat or prevent Leber hereditary optic neuropathy.
5. Clinical trials are underway evaluating these proposed treatments.

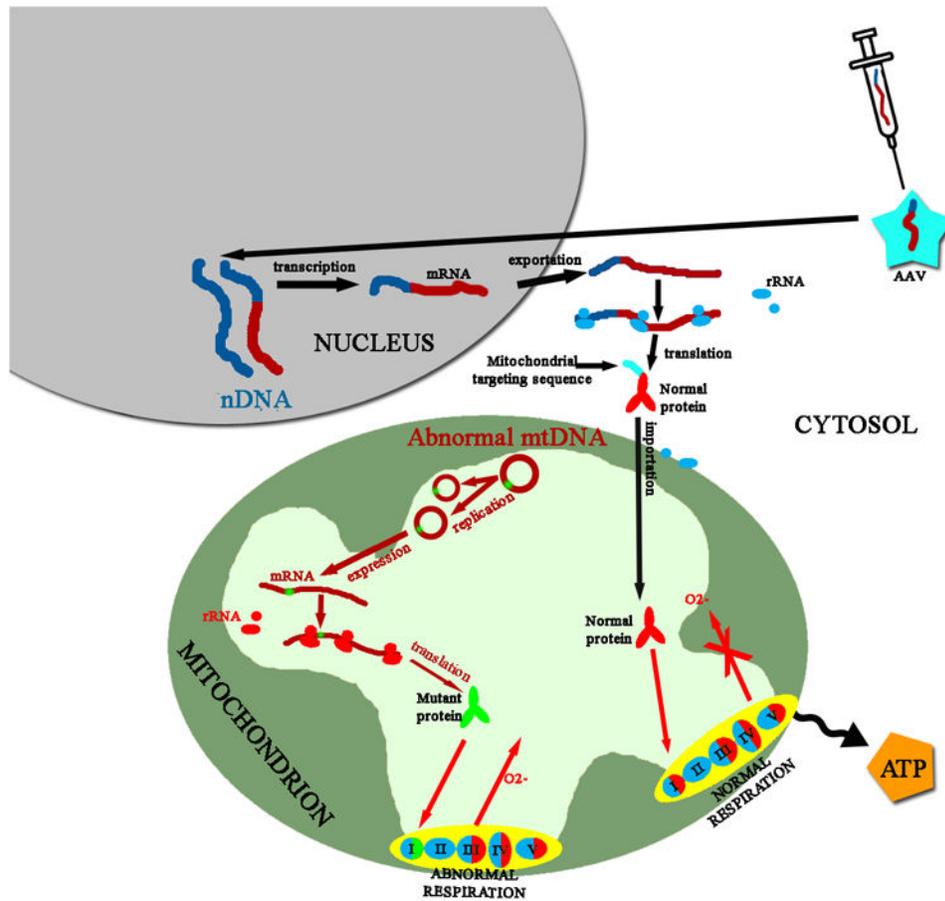


Figure 1. Allotropic rescue

In this form of gene therapy viral vectors are used to insert exogenous DNA into the nucleus. This genetic material is transcribed and then translated, creating a new protein in the cytosol. The protein contains a mitochondrial targeting sequence (light blue line), which leads to the protein's importation within the defective mitochondrion. This new protein (red) then becomes incorporated in the respiratory chain, replacing the abnormal protein (green), improving its function and preventing formation of free radicals, leading to survival of the cell. (Adapted with permission from original drawings by Cédric Lamirel, M.D.)

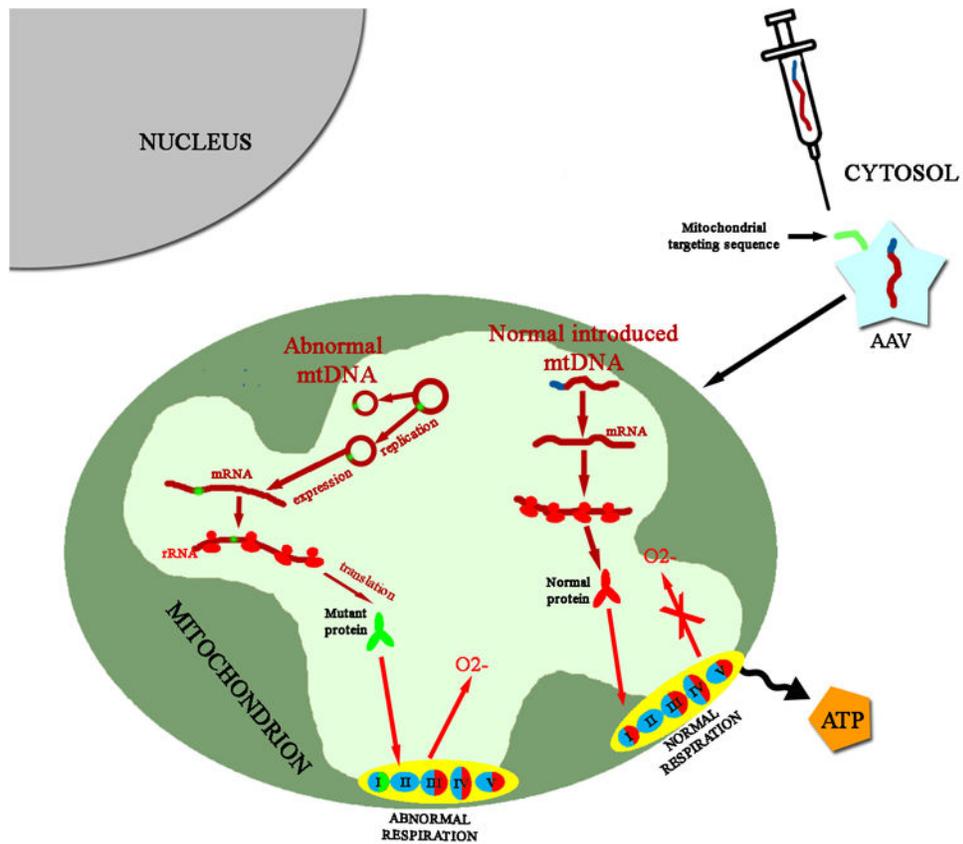


Figure 2. Mitochondrial DNA incorporation

In this form of gene therapy, a viral vector has a mitochondrial targeting sequence attached to it (green line). The normal DNA contained within this vector is delivered directly to the defective mitochondrion, where a promoter allows mitochondrial transcription and translation to occur. The normal protein then becomes incorporated into the respiratory chain, improving its function and preventing formation of free radicals, leading to survival of the cell. (Adapted with permission from original drawings by Cédric Lamirel, M.D.)

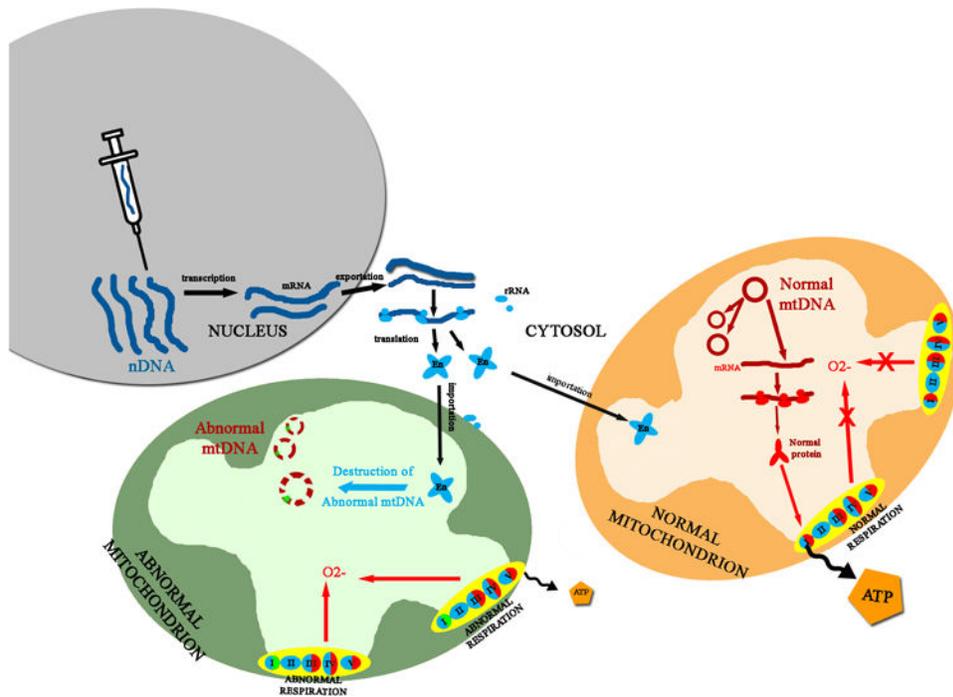


Figure 3. Gene shifting

In gene shifting, exogenous DNA is incorporated into the nuclear genome through a viral vector. Once incorporated, the genetic material is transcribed, and then translated into an endonuclease targeted for delivery to the mitochondria. In cells that are heteroplasmic for mitochondrial DNA mutations (yellow mitochondrion = normal, green mitochondrion = abnormal mitochondrion with mutated DNA) the endonuclease selectively degrades the abnormal DNA, leading to only normal mitochondria remaining within the cell. This limits the formation of damaging reactive oxygen species. The usefulness of this technique to treat Leber hereditary optic neuropathy is limited as most affected patients are homoplasmic for the mitochondrial DNA mutations. (Adapted with permission from original drawings by Cédric Lamirel, M.D.)

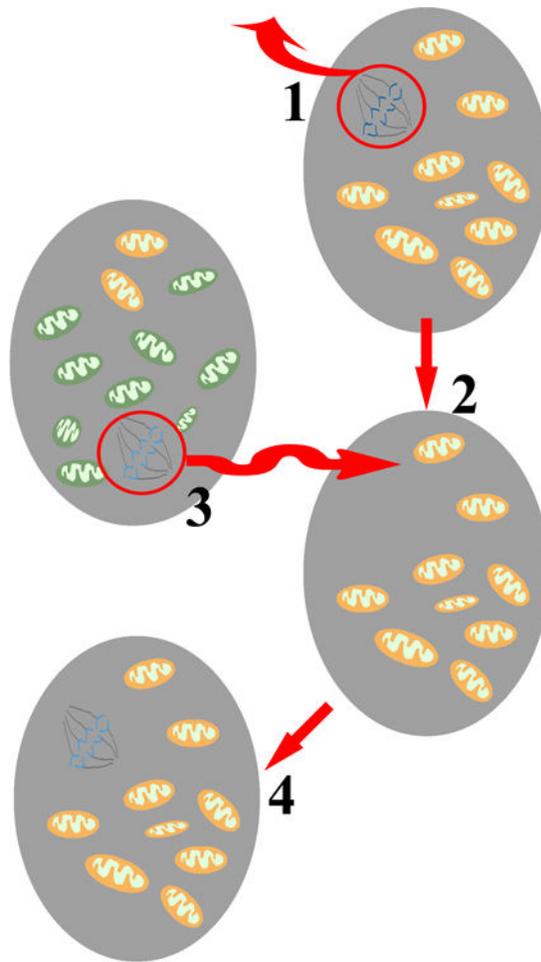


Figure 4. Nuclear Transfer

One technique of nuclear transfer involves removing the nuclear material from an unfertilized oocyte that does not harbor a mitochondrial mutation (1) so that the cell becomes enucleated (2). The nuclear material from an affected oocyte is removed (3) and placed into the enucleated cell with normal mitochondria. The result is an oocyte with normal mitochondria but with the nuclear genetic material from the affected oocyte (4). This oocyte can then undergo in vitro fertilization. (Adapted with permission from original drawings by Cédric Lamirel, M.D.)