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Review

Advances in the treatment of mitochondrial epilepsies

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ABSTRACT

Epilepsy is frequently a severe and sinister symptom in primary mitochondrial diseases, a group of more than 350 different genetic disorders characterized by mitochondrial dysfunction and extreme clinical and biochemical heterogeneity. Mitochondrial epilepsy is notoriously difficult to manage, principally because the vast majority of primary mitochondrial diseases currently lack effective therapies. Treating the underlying mitochondrial disorder is likely to be a more effective strategy than using traditional antiepileptic drugs. This review, initially presented at the 7th London-Innsbruck Colloquium on Status Epilepticus and Acute Seizures at the Francis Crick Institute in London, summarizes the currently available and emerging therapies for mitochondrial epilepsy. Potentially treatable mitochondrial diseases include disorders of coenzyme Q_{10} biosynthesis and a group of mitochondrial respiratory chain complex I subunit and assembly factor defects that respond to riboflavin (vitamin B2). Approaches that have been adopted in actively recruiting clinical trials include redox modulation, harnessing mitochondrial biogenesis, using rapamycin to target mitophagy, nucleoside supplementation, and gene and cell therapies. Most of the clinical trials are at an early stage (Phase 1 or 2) and none of the currently active trials is specifically targeting mitochondrial epilepsy.

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1. Introduction

Primary mitochondrial diseases have recently been redefined as disorders caused by mutations that "primarily or secondarily lead to oxidative phosphorylation (OXPHOS) dysfunction or other disturbances of mitochondrial structure and function including perturbed mitochondrial ultrastructure, aberrant synthesis of cofactors and vitamins, or other impaired metabolic processes within the mitochondrion" [1]. Epilepsy is reported to affect up to 40% of patients with primary mitochondrial disease [2] and is often a late and sinister clinical feature; 50% of affected patients died within 9 months after seizure onset in one cohort [3]. Unfortunately, there are currently no effective therapies for the vast majority of mitochondrial diseases, and this includes the mitochondrial epilepsies. This brief review, originally presented on April 9, 2019 at the 7th London-Innsbruck Colloquium on Status Epilepticus and Acute Seizures at the Francis Crick Institute in London, summarizes the currently available treatments for mitochondrial epilepsy and emerging therapies either undergoing clinical trial or on the horizon.

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2. Antiepileptic drugs and supportive management

Many mitochondrial epilepsies are notoriously resistant to antiepileptic drugs (AEDs), and some have been reported to be resistant to many different combinations of drugs. There continue to be anecdotal case reports and small case series reporting benefit of specific AEDs in patients with mitochondrial epilepsies (e.g., [4,5]), but the clinical, biochemical, and genetic heterogeneity of mitochondrial epilepsies, and the unpredictable natural course makes interpretation of such reports extremely challenging. In an ideal world the primary treatment should clearly be directed at the underlying cause rather than waiting to treat seizures when they occur. However at present, there are no disease-modifying therapies for the vast majority of mitochondrial diseases, and supportive treatments remain the principal therapies offered to affected patients. These include AEDs and treatment of multisystemic disease complications when they occur [6].

3. Cofactor and vitamin responsive disorders

There are some notable exceptions of primary mitochondrial disorders where disease-modifying therapies do exist, and it is important to recognize these disorders promptly. The most well-known subgroup comprises disorders of coenzyme Q_{10} (ubiquinone) biosynthesis, which at least in theory are likely to be ameliorated by supplementation with pharmacological doses of coenzyme Q_{10} [7]. Coenzyme Q_{10} functions as a mobile electron carrier within the respiratory chain, as well as being a potent antioxidant. Coenzyme Q_{10} at 30 mg/kg/day was reported to prevent renal impairment in a child with *COQ2* mutations whose sibling had end-stage renal failure, seizures, stroke-like episodes and cognitive impairment [8]. However, a more recent report described progressive neurological dysfunction, including seizures and encephalopathy, in patients with COQ2 deficiency whose initial symptoms of diabetes and nephrotic syndrome had responded to coenzyme Q_{10} supplementation in the neonatal period [9]. Progression of neurological disease may be because of limited intracerebral bioavailability of coenzyme Q_{10}. Another issue is that other coenzyme Q_{10} biosynthesis defects, particularly *COQ4* and *COQ9* mutations, appear to have prenatal onset and are associated with severe disease progression and early death, despite prompt initiation of coenzyme Q_{10} supplementation [10–13], so other treatment strategies may be needed for this group of disorders.

Another group of potentially treatable mitochondrial disorders are those that respond to supplementation with riboflavin (vitamin B2) [14]. These include some complex I deficiencies, particularly mutations of *ACAD9*, encoding a flavoprotein required for complex I assembly. Affected patients typically have a good clinical response to riboflavin supplementation [15]. The most frequent clinical features associated with ACAD9 deficiency are hypertrophic cardiomyopathy, lactic acidosis, and exercise intolerance, but seizures have been reported in occasional cases [16,17]. Mutations of *AIFM1*, encoding apoptosis inducing factor mitochondria associated 1, another flavoprotein required for complex I assembly, have been reported to cause riboflavin-responsive ataxia in two patients [18]; *AIFM1* mutations have also been associated with seizures, but riboflavin therapy was not reported in these individuals [19]. Riboflavin may also be beneficial in other complex I deficiencies, particularly mutations of the NDUFV1 and NDUFV2 subunits, which are flavoproteins interacting with the flavin mononucleotide (FMN) active cofactor of the complex I holoenzyme [14].

The role of vitamins and cofactors in other mitochondrial disorders is uncertain. There have been very few randomized clinical trials in primary mitochondrial diseases, and a Cochrane review published in 2012 concluded that further research is needed in this area [20].

4. Development of novel therapies

Development of novel therapies for mitochondrial disease is a growth industry. However, despite more than 2000 publications per year on mitochondrial disease treatment there are currently no licensed treatments for systemic mitochondrial disease. Why is it so difficult to treat mitochondrial disease? The multilayered complexity of mitochondrial disease, with extreme clinical, biochemical, and genetic heterogeneity, provides an enormous barrier to therapy development. However, despite these difficulties, a large number of candidate therapies is currently in development [1,21].

Novel therapies in development for mitochondrial disease may be divided broadly into two groups: pharmacological and genetic treatments. Many of the pharmacological approaches are generic 'disease agnostic' approaches and include targeting reactive oxygen species, stabilizing the mitochondrial membrane, harnessing mitochondrial biogenesis, and targeting mitophagy (Fig. 1).

4.1. Antioxidant approaches

Antioxidants have played a central role in the (attempted) treatment of mitochondrial disease for decades, although evidence for their efficacy remains limited at present [20]. The central tenet underlying their use is that impairment of mitochondrial function, especially of complexes I and III, leads to excessive generation of reactive oxygen species (ROS), which in turn leads to a vicious cycle of further mitochondrial damage, including lipid, protein, and DNA peroxidation. Reactive oxygen species include the superoxide radical and hydrogen peroxide. Accumulating evidence implicating ROS in seizure generation outside the context of primary mitochondrial disease [22,23] supports the continuing use of antioxidants in mitochondrial epilepsies, in the absence of more specific disease-modifying therapies. A word of caution is that ROS are not merely damage-inducing molecules but rather have important physiological roles in the mitochondrion and in the cell, especially in interorganellar signaling [24]. One study suggested that excessive antioxidant exposure could be harmful in a mouse model of mitochondrial disease; a muscle-specific *COX15* knockout had worse survival following *N*-acetylcysteine (NAC) therapy [25]. The antioxidants used in clinical practice include coenzyme Q_{10}, NAC, and vitamins E and C. Newer

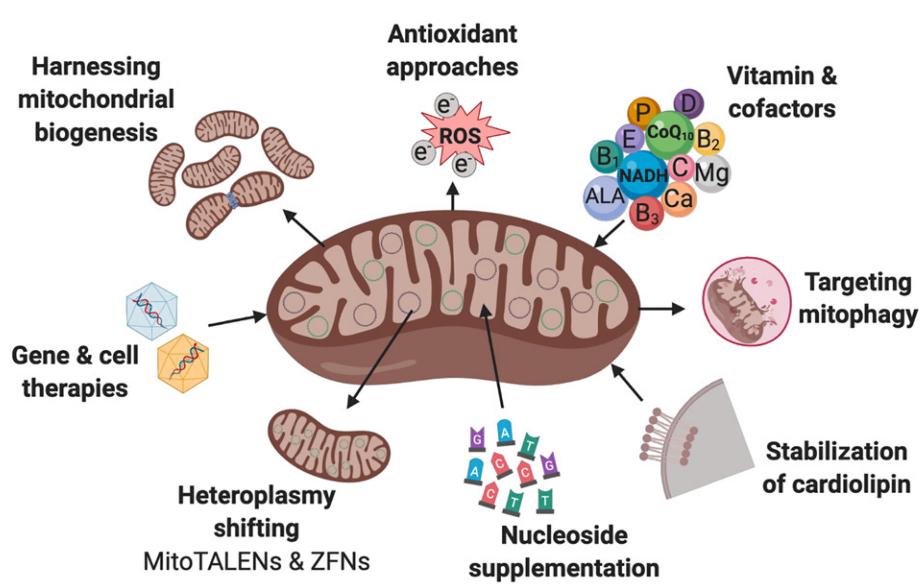

Fig. 1. Emerging therapies for mitochondrial disease. Approaches to treat primary mitochondrial diseases that are currently in development include redox modulation using antioxidants, harnessing mitochondrial biogenesis, stabilizing the mitochondrial membrane lipid cardiolipin with elamipretide, targeting mitophagy using rapamycin, nucleoside supplementation to bypass the molecular defect in thymidine kinase 2 deficiency, heteroplasmy shifting using MitoTALENs and zinc finger nucleases, and gene and cell therapies.

antioxidants that have been investigated in preclinical studies include EPI-743 and KH176. Open-label studies of EPI-743 in the mitochondrial encephalomyelopathy Leigh syndrome did not conclusively demonstrate benefit [26,27]. The KHENERGY study, a double-blind, randomized, placebo-controlled, two-way crossover phase IIA study of KH176, demonstrated tolerability and safety in adult patients with relatively mild multisystemic disease related to the m.3243A>G mutation (average heteroplasmy 61% in urinary epithelial cells, 18% in leukocytes) [28]. A phase III study is planned but not yet active.

4.2. Harnessing mitochondrial biogenesis

The process of making new mitochondria, known as mitochondrial biogenesis, is ultimately regulated by the master transcriptional coactivator PGC1α, which interacts with multiple transcription factors including the nuclear respiratory factors NRF1 and NRF2 and the peroxisome proliferator-activated receptors (PPARs), leading to increased transcription of hundreds of genes encoding mitochondrial components including OXPHOS subunits and assembly factors and fatty acid oxidation enzymes [29]. Theoretically, increasing mitochondrial mass by stimulating mitochondrial biogenesis should result in a net increase in energy production and thus potentially ameliorate at least some of the effects of mitochondrial dysfunction. Several therapeutic approaches have attempted to manipulate this process by activating PGC1α by modulating its acetylation (e.g., by activating the SIRT1 deacetylase) or phosphorylation (e.g., via the adenosine monophosphate (AMP)-activated protein kinase) or by increasing PGC1α target molecules such as the PPARs (e.g., with decanoic acid). As with antioxidant therapies, evidence for efficacy of these approaches is currently limited. Initial studies of bezafibrate, resveratrol, and 5-Aminoimidazole-4-carboxamide ribonucleotide (AICAR) in animal models yielded conflicting data [30]. A clinical trial of resveratrol in mitochondrial myopathies is ongoing (NCT03728777, Table 1), and a trial of bezafibrate has recently completed but is yet to report its results (NCT02398201, clinicaltrials.gov). We observed promising preclinical data in human patient cell models of complex I deficiency treated with decanoic acid (C10) [31], but this has not yet been translated into a clinical trial for primary mitochondrial disease. Increasing nicotinamide adenine dinucleotide (NAD+), either by supplementing with the vitamin B3 derivative nicotinamide riboside or by inhibiting poly(adenosine diphosphate(ADP)-ribose) polymerase 1 (PARP1, which consumes NAD+), may also promote mitochondrial biogenesis by activating SIRT1. Increasing NAD+ availability ameliorated the phenotypes of two mouse models of mitochondrial disease [32,33], and improved mitochondrial function in human complex I deficient fibroblasts [34]. Two actively recruiting trials are investigating an NAD+ modulator KL 1333 (NCT03888716) and nicotinamide riboside (NCT03432871) while a third aims to use a novel PPAR agonist REN001 (NCT03862846) to increase mitochondrial biogenesis (Table 1). It is interesting to note that all of the active trials investigating mitochondrial biogenesis as a therapeutic strategy are targeting mitochondrial myopathies; none are aiming to treat mitochondrial epilepsies, possibly because of the challenges inherent in targeting molecules to the central nervous system.

4.3. Targeting mitophagy

Inhibition of the mammalian target of rapamycin (mTOR) pathway by rapamycin has been used to target mitophagy, the process of selective elimination of dysfunctional mitochondria. Several recent preclinical studies have reported beneficial effects of rapamycin in treating mitochondrial disease; high-dose intraperitoneal rapamycin increased survival and attenuated the neurological phenotype and brain lesions of *Ndufs4* −/− mice, a murine model of Leigh syndrome, and also improved the phenotype of myopathic 'deletor' mice harboring a mutation in the twinkle DNA helicase, while low-dose rapamycin increased survival of Tk2 deficient mice [35–37]. In contrast, there was no evidence of benefit from rapamycin in an encephalomyopathic mouse model harboring a homozygous nonsense mutation in the coenzyme Q_{10} biosynthetic factor Coq9 [38]. Switching immunosuppression from calcineurin inhibitors to mTOR inhibitors was reported to lead to clinical improvement in four renal transplant patients with mitochondrial disease related to the m.3243A>G mutation (associated with mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes, MELAS) [39]. Recently investigators in New York treated two patients with mitochondrial seizures with everolimus, a rapamycin analogue. The authors reported apparent benefit of everolimus in the first child, who had Leigh syndrome caused by a homozygous *NDUFS4* mutation, but the second child, who had m.3243A>G MELAS, had progressive disease despite everolimus therapy and subsequently died [40]. The mechanisms underlying the potential efficacy of rapamycin in mitochondrial disease remain unknown. Modulation of mitophagy is the most favored mechanism but other possibilities include increased lysosomal biogenesis and metabolic reprogramming to reduce the dependence on OXPHOS [40]. The mTOR pathway has also been linked to folate availability, which is interesting since folate is a key player in one-carbon metabolism, a metabolic pathway implicated in the pathogenesis of mitochondrial disease [36,41,42]. The variable findings of the preclinical and compassionate use data suggest that rapamycin may not be a universal panacea for mitochondrial disease. A formal clinical trial is needed to determine which patients may benefit from rapamycin or everolimus and to establish the lowest efficacious dose, in view of the known adverse effects associated with these drugs, including immunosuppression and hyperlipidemia. A clinical trial of NAB-sirolimus (nanoparticle albumin-bound rapamycin) in genetically confirmed Leigh syndrome is currently active although not yet recruiting patients (NCT03747328, Table 1).

4.4. Hypoxia

A genome-wide clustered regularly interspaced short palindromic repeats (CRISPR) screen identified the Von Hippel Lindau (VHL) ubiquitin ligase as a key factor rescuing mitochondrial dysfunction in a cellular model, thus implicating the hypoxia inducible factor (HIF) transcriptional pathway as a therapeutic target in mitochondrial disease [43]. The authors went on to demonstrate that maintaining the *Ndufs4* −/− Leigh syndrome mice in chronic hypoxic conditions (11% O_2) prolonged survival and attenuated the brain lesions observed in these mutant mice [43]. A more recent study by the same group has shown that the mechanism of neuroprotection by hypoxia in the *Ndufs4* −/− mouse is by prevention of brain tissue hyperoxia rather than by activation of the HIF pathway [44]. Chronic hypoxia is obviously not a therapy of choice for human patients, so clinical translation of this treatment will be challenging. However, an immediate clinical message is that hyperoxia should be avoided in patients with mitochondrial disease in the intensive care unit [45,46], including those with mitochondrial status epilepticus.

4.5. Other pharmacological approaches

Another pharmacological approach is to stabilize the inner mitochondrial membrane lipid milieu in which the OXPHOS complexes and supercomplexes are embedded, in order to preserve mitochondrial function. Elamipretide (SS-31, MTP-131) is a Szeto-Schiller tetrapeptide (D-Arg-dimethylTyr-Lys-Phe-NH2) that appears to stabilize cardiolipin, the major lipid component of the inner mitochondrial membrane. A recently completed clinical trial of elamipretide in adults with primary mitochondrial myopathy, the MMPOWER study, reported improvements in the 6-minute walk test after 5 days of treatment [47]. A phase 3 double-blind placebo-controlled trial of elamipretide in mitochondrial myopathy is due to start recruiting patients shortly (NCT03323749, Table 1). Intriguingly, the small molecule nature of

Table 1
Selection of currently active interventional trials for primary mitochondrial disorders.

Agent (other names)	Trial number	Mechanism of action	Disorder	Age range	Design	Primary outcome measures	Status	Sponsor	Type of study
KL 1333	NCT03888716	NAD+ modulator (mitochondrial biogenesis)	• Mitochondrial diseases • Mitochondrial respiratory chain deficiencies • MELAS syndrome • Mitochondrial myopathies	18–75y	Phase 1a/1b Randomized, placebo-controlled	Safety	Recruiting	NeuroVive	Industry
Nicotinamide riboside	NCT03432871	Increase NAD+ (mitochondrial biogenesis)	• Mitochondrial diseases • Mitochondrial myopathies • Progressive external ophthalmoplegia • Mitochondrial DNA deletion • MELAS	18–70y	Phase 1 Open label	Bioavailability, safety, mitochondrial biogenesis (assessed by muscle biopsy)	Recruiting	Cambridge University Hospitals NHS Foundation Trust, UK	Investigator led
REN001	NCT03862846	PPARδ agonist (mitochondrial biogenesis)	• Primary mitochondrial myopathy	≥16y	Phase 1 Open label	Safety and tolerability (assessed by number of participants with adverse events)	Recruiting	Reneo Pharma Ltd	Industry
Resveratrol	NCT03728777	Mitochondrial biogenesis	• Mitochondrial myopathies	18-80y	Double-blind, randomized, placebo-controlled, cross-over study	Decrease in heart rate during constant load cycling exercise	Recruiting	Rigshospitalet, Denmark	Investigator led
Sodium phenylbutyrate	NCT03734263	Stabilization of PDHc enzyme	• PDHc deficiency	3 m-18y	Phase 1/2 Open label	Blood lactate level	Recruiting	Fondazione Telethon	Investigator led
Dichloroacetate	NCT02616484	Decrease inactivation of PDHc by inhibiting PDK	• PDHc deficiency	6 m-17y	Phase 3 Randomized, placebo-controlled, quadruple-masked, crossover study	Observer reported outcome (ObsRO) measure of health	Recruiting	University of Florida, Columbia University, Medosome Biotec LLC, Saol Therapeutics	Investigator led/ Industry
scAAV2-P1ND4v2	NCT02161380	Adeno-associated virus vector gene therapy	• LHON	≥15y	Phase 1 Open-label dose escalation study	Toxicity	Recruiting	John Guy, National Eye Institute, University of Miami	Investigator led
AHSCT	NCT02427178	Allogeneic hematopoietic stem cell transplant	• MNGIE	5-55y	Phase 1	Engraftment success (neutrophil count)	Recruiting	Michio Hirano, Cornell University, National Institute of Neurological Disorders and Stroke	Investigator led
MT1621 (Combination pyrimidine nucleosides)	NCT03845712	Nucleoside supplementation	• TK2 deficiency	All ages	Phase 2 Open-label extension	Safety	Enrolling by invitation	Modis Therapeutics, Inc.	Industry
Autologous CD34+ hematopoietic stem cells enriched with MNV-BLD	NCT03384420	'Mitochondria augmentation therapy'	• Pearson syndrome	All ages	Phase 1/2	Number of participants with treatment-related adverse events	Enrolling by invitation	Minovia Therapeutics Ltd.	Industry
EPI-743 (Vincerinone)	NCT02352896	Antioxidant	• Leigh syndrome	1-18y	Phase 2 Open label	Long term effect on disease severity (NPMDS)	Active, not recruiting	Edison Pharmaceuticals Inc.	Industry
EPI-743 (Vincerinone)	NCT01370447	Antioxidant	• Mitochondrial diseases	≥1y	Phase 2 Open label	Change in neuromuscular function, adverse events, NPMDS score	Active, not recruiting	Edison Pharmaceuticals Inc.	Industry
EPI-743 (Vincerinone)	NCT01642056	Antioxidant	• Mitochondrial disease	2-11y	Phase 1/2 Nonrandomized, double-blind, placebo-controlled crossover	NPMDS score	Active, not recruiting	National Human Genome Research Institute	Investigator led
NAB-Sirolimus (ABI-009)	NCT03747328	Targeting mitophagy	• Leigh syndrome (genetically confirmed)	2-17y	Phase 2A Open label	Number of participants with adverse events, GMFM	Active, not yet recruiting	Aadi, LLC	Industry
Elamipretide	NCT03323749	Stabilization of	• Primary	16-80y	Phase 3	6MWT, PMMSA	Active,	Stealth	Industry

Table 1 (*continued*)

Agent (other names)	Trial number	Mechanism of action	Disorder	Age range	Design	Primary outcome measures	Status	Sponsor	Type of study
(MTP-131)		cardiolipin	mitochondrial myopathy		Randomized, double-blind, parallel-group, placebo-controlled	fatigue score	not yet recruiting	BioTherapeutics Inc.	
L-citrulline	NCT03952234	Nitric oxide precursor	• MELAS	18-65y	Phase 1 Dose-finding	Incidence of dose limiting toxicities, to establish maximum tolerable dose	Active, not yet recruiting	Baylor College of Medicine, National Institutes of Health (NIH), University of South Florida, Columbia University	Investigator led
Erythrocyte encapsulated thymidine phosphorylase (EE-TP)	NCT03866954	Enzyme replacement	• MNGIE	≥12y	Phase 2 Open label (sequential assignment)	Safety	Active, not yet recruiting	St George's, University of London, The Clinical Trial Company, Orphan Technologies Ltd	Investigator led/Industry

Key: 6MWT, six-minute walk test; AHSCT, allogeneic hematopoietic stem cell transplant; GMFM, gross motor function measure; m, months; LHON, Leber hereditary optic neuropathy; MELAS, mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes; MNGIE, mitochondrial neurogastrointestinal encephalomyopathy; NPMDS, Newcastle pediatric mitochondrial disease scale; PDHc, pyruvate dehydrogenase complex; PDK, pyruvate dehydrogenase kinase; PMMSA, Primary Mitochondrial Disease Symptom Assessment; TK2, thymidine kinase 2; y, years.

elamipretide means that it is able to cross the blood–brain barrier (BBB) [48], which makes it potentially a relevant molecule to treat mitochondrial epilepsies.

Stroke-like episodes (SLEs) are increasingly recognized to represent seizure activity. Management of the canonical mitochondrial stroke syndrome MELAS is extremely challenging [49]. Agents which have aimed to address SLEs in MELAS include L-arginine, L-citrulline, L-taurine, and succinate, but high level evidence of efficacy is currently lacking. Nitric oxide deficiency has been implicated in the pathogenesis of SLEs, and there was apparent benefit of the nitric oxide precursor L-arginine in both prevention and amelioration of SLEs in a series of open-label studies performed in Japan [50,51]. As a consequence of these open-label studies, L-arginine use in MELAS has become widespread across the globe even though a randomized placebo-controlled trial has never been performed. A dose-finding study of L-citrulline, another precursor of nitric oxide, in MELAS is currently in progress (NCT03952234, Table 1).

Nucleosides have shown efficacy in preclinical trials to treat myopathic mitochondrial DNA depletion syndrome (MDDS) caused by thymidine kinase 2 (TK2) deficiency [52], and a compassionate use study recently reported beneficial effects in affected children and adults [53]. A Phase 2 open-label extension of combination pyrimidine nucleosides in TK2 deficiency is ongoing (NCT03845712). The ability of nucleosides to penetrate the BBB is not known, and whether these molecules would successfully treat seizures in encephalomyopathic forms of MDDS remains controversial.

4.6. Genetic and cellular therapies

Genetic therapies need to target the mitochondrial DNA (mtDNA) or nuclear genome, depending on the specific mitochondrial disorder. Adeno-associated viral (AAV) vector-mediated gene therapy has been reported in several preclinical models of nuclear-encoded mitochondrial disease, including mouse models of mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) and ETHE1, MPV17, and NDUFS4 deficiencies [54–57]. These have shown generally positive effects and could potentially be a useful therapeutic strategy for all nuclear-encoded mitochondrial diseases. However, the limiting factor at present is the enormous expense and time requirement to develop and treat preclinical models for >300 different gene defects. Unless new methods are developed to scale up these treatments, or regulatory agencies relax the preclinical therapy requirements in some way, it is unrealistic to expect that gene therapy will ever be available for the large number of ultra-rare mitochondrial gene defects affecting only a few individuals each worldwide. Clustered regularly interspaced short palindromic repeats (CRISPR)-based gene editing was used to rescue mitochondrial dysfunction in an induced pluripotent stem cell model of coenzyme Q_{10} deficiency [58], and this may be another therapeutic strategy for nuclear-encoded mitochondrial diseases going forwards.

Targeting the mitochondrial genome is more challenging, since it is relatively inaccessible owing to its protected position within the mitochondrion, encased by two lipid membranes. However, recent approaches using mitochondrial Transcription activator-like effector nucleases (TALENs) and zinc finger nucleases to target and selectively eliminate mutant mtDNA sequences have shown benefit in both cell and animal models of heteroplasmic mtDNA disease [59–62]. A concern is that selective destruction of mutant mtDNA at high heteroplasmy level may lead to a temporary state of mtDNA depletion before the wild-type mtDNA recovers to normal copy numbers, and patients would be extremely vulnerable during this recovery period. Strategies to tackle this problem are awaited, but it is theoretically possible that nucleoside supplementation may hasten the recovery of the wild-type mtDNA in this situation.

Another gene therapy approach, currently in clinical trial, is to treat Leber hereditary optic neuropathy (LHON) by intraocular injection of AAV2-ND4 recoded in the nuclear genetic code so that it can be expressed from the nucleus, the recombinant protein being synthesized on cytosolic ribosomes and subsequently imported into the mitochondrion (NCT02161380, Table 1) [63]. How this could be adapted for treatment of mitochondrial epilepsies, which would need at least systemic gene therapy if not intrathecal or intracerebroventricular injection, remains to be determined.

Organ transplantation as a genetic rescue for mitochondrial disease has been explored for MNGIE using either allogeneic hematopoietic stem cell transplantation (AHSCT - NCT02427178, Table 1) or liver transplantation, and for ETHE1 deficiency (liver transplantation) [64–66]. A trial of erythrocyte-encapsulated thymidine phosphorylase enzyme replacement therapy in MNGIE is about to start recruiting patients (NCT03866954, Table 1) [67]. Another study is examining the effects of transplantation of autologous CD34+ hematopoietic stem cells enriched with maternal blood-derived mitochondria (MNV-BLD) in children with the Pearson marrow pancreas syndrome (NCT03384420).

5. Concluding remarks

Recent years have seen a dramatic increase in the number of novel therapies under development for primary mitochondrial disease. At the time of writing (24 August 2019) a search for 'mitochondrial diseases' identified 215 trials in clinicaltrials.gov, of which at least 8 are interventional studies actively recruiting patients (Table 1). Although none of the active trials are specifically targeting mitochondrial epilepsy, this is an exciting time for mitochondrial disease, and the possibility of effective therapies for these devastating disorders is finally on the horizon.

Declaration of competing interest

The author declares that she has no conflicts of interest relating to this manuscript.

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