Terapie farmacologiche e nuove prospettive terapeutiche nelle malattie mitocondriali

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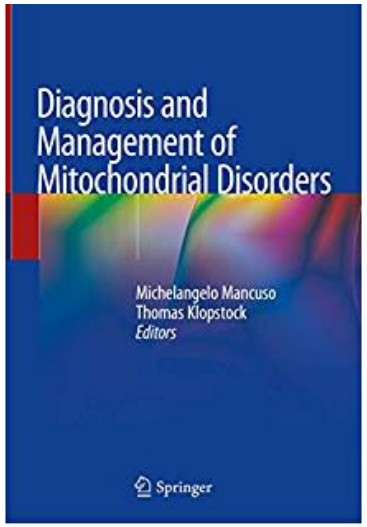
Sin
SOCIETÀ ITALIANA DI NEUROLOGIA

1. TERAPIE E RACCOMANDAZIONI

2. APPROCCI SPERIMENTALI E TRIAL READINESS



PRIMARY MITOCHONDRIAL DISEASES

TERAPIE E RACCOMANDAZIONI

1.TERAPIA PALLIATIVA

2.TERAPIA FARMACOLOGICA

- Rimuovere metabolite tossici
- Aiiutare la respirazione mt con intermedi e cofattori
- Supplementazione vitaminica
- Combattere lo stress ossidativo (ROS), antiossidanti
- “Farmaci pericolosi”

3. RACCOMANDAZIONI E CONSENSUS

1.TERAPIA PALLIATIVA

- SNC: controllo crisi epilettiche
- Muscolo: PEO (blefaroplastica), integratori, esercizio
- Occhio: chirurgia cataratta. Idebenone Leber
- Sangue: transfusione nell'anemia sideroblastica
- Sistema endocrino: curare il DM, la tiroide, la disfunzione paratiroidi…
- Cuore: pacemaker, anti aritmici; trapianto
- GI: alimentazione; PEG
- Orecchio: impianto cocleare; (aminoglycosides)

2. Tp farmacologica

Journal of *Clinical Medicine*

MDPI

Review

Therapeutical Management and Drug Safety in Mitochondrial Diseases—Update 2020

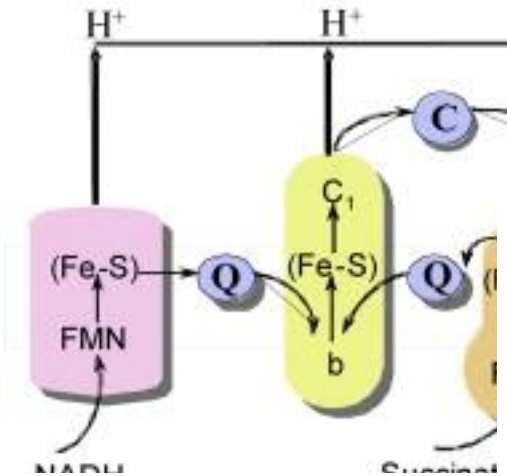
Francesco Gruosso, Vincenzo Montano, Costanza Simoncini, Gabriele Siciliano and Michelangelo Mancuso *

- Current treatment for PMD is largely supportive and mainly includes vitamins and cofactors supplements
  - Antioxidants: coenzyme Q10, idebenone, vitamin C, vitamin E
  - Respiratory chain cofactors: thiamine, riboflavin niacin
  - Compounds that correct secondary biochemical deficiencies: carnitine and creatine
  - Improve lactic acidosis: dichloroacetate (peripheral nerve toxicity!)
- Exercise

2. MITO-COCKTAIL

- Coenzima Q10 ed analoghi (dosaggio variabile: 200-1000 mg\die)
- Riboflavina 100-200 mg\die
- Vitamina B
- L-carnitine
- Creatine
- IDEBENONE IN LHON

Coenzyme q10



NEUROLOGICAL REVIEW

Heterogeneity of Coenzyme Q_{10} Deficiency

Patient Study and Literature Review

Valentina Emmanuele, MD; Luis C. López, PhD; Andres Berardo, MD; Ali Naini, PhD; Saba Tadesse, BS; Bing Wen, MD; Erin D'Agostino, BA; Martha Solomon, BA; Salvatore DiMauro, MD; Catarina Quinzii, MD; Michio Hirano, MD

Neuromuscular Disorders 20 (2010) 44–48

Contents lists available at ScienceDirect

Neuromuscular Disorders

journal homepage: www.elsevier.com/locate/nmd

- Coenzyme Q10
  - Uniquinol seems to be better than ubiquinone
  - solubilized formulations of CoQ10 superior bioavailability
  - bioavailability of CoQ10 is dependent on the type and amounts of oil in the formulations as well as by its delivery system, in the following order: nanoparticulated, solubilized, oil-emulsioned and powder (which is only minimally absorbed)

tients

rmé [c], Odile Rigal [d],
no [f], Paola Tonin [g],

France

Cofactors

Niacin or Vitamin B3

- Niacin (Vitamin B3) is a precursor of nicotinamide adenine dinucleotide (NADH), which is the primary electron donor for respiratory chain complex I, whose enzymatic name is NADH dehydrogenase and converts NADH to NAD.
- It has been shown that vitamin B3 supplementation in the form of niacin helps to restore cellular NADH/NAD balance and enhance mitochondrial biogenesis in human fibroblasts from a complex I disease patient, and to improve survival in a respiratory chain complex I disease Caenorhabditis elegans animal model

Effective treatment of mitochondrial myopathy by nicotinamide riboside, a vitamin B3

Nahid A Khan[1], Mari Auranen[1,2,†], Ilse Paetau[1,†], Eija Pirinen[3,4], Liliya Euro[1], Saara Forsström[1], Lotta Pasila[1], Vidya Velagapudi[5], Christopher J Carroll[1], Johan Auwerx[3] & Anu Suomalainen[1,2,6,*]

Highlights

- Mitochondrial myopathy patients have NAD^+ deficiency in muscle and blood
- Niacin is an efficient NAD^+ booster in humans
- Niacin improves muscle strength and fatty liver in mitochondrial myopathy
- Niacin boosts muscle mitochondrial biogenesis and respiratory chain activity in humans

Clinical and Translational Report

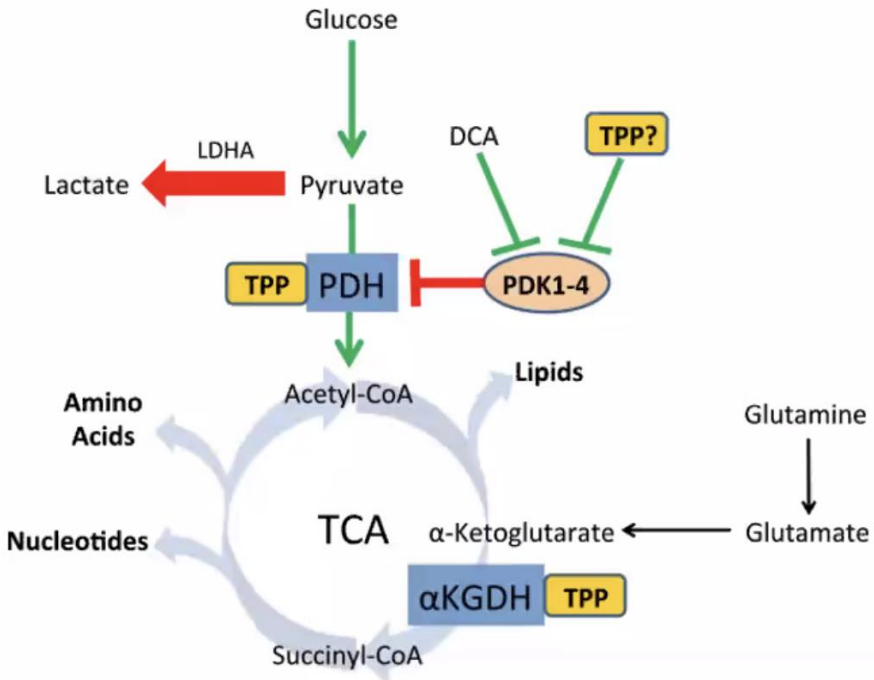
Niacin Cures Systemic NAD^+ Deficiency and Improves Muscle Performance in Adult-Onset Mitochondrial Myopathy

Eija Pirinen,[1,*] Mari Auranen,[2,3,13] Nahid A. Khan,[2,13] Virginia Brilhante,[2] Niina Urho,[3] Alberto Pessia,[4] Antti Hakkarainen,[5,6] Juho Kuula,[5] Ulla Heinonen,[3] Mark S. Schmidt,[7] Kimmo Haimilahti,[1] Päivi Piirilä,[8] Nina Lundbom,[5] Marja-Riitta Taskinen,[1] Charles Brenner,[7] Vidya Velagapudi,[4,14] Kirsi H. Pietiläinen,[9,10] and Anu Suomalainen[2,11,12,15,*]

Cofactors

Thiamin or Vitamin B1

- Thiamine (Vitamin B1) is a cofactor of alpha-ketoacid dehydrogenases, including the pyruvate dehydrogenase complex (PDHC).
- Thiamine has been used in mitochondrial disorders individually or in combination with other agents.



Thiamine dosage: < 3y 150 mg/die
> 3y 300 mg/die

Or

10-40 mg/Kg in pediatrics

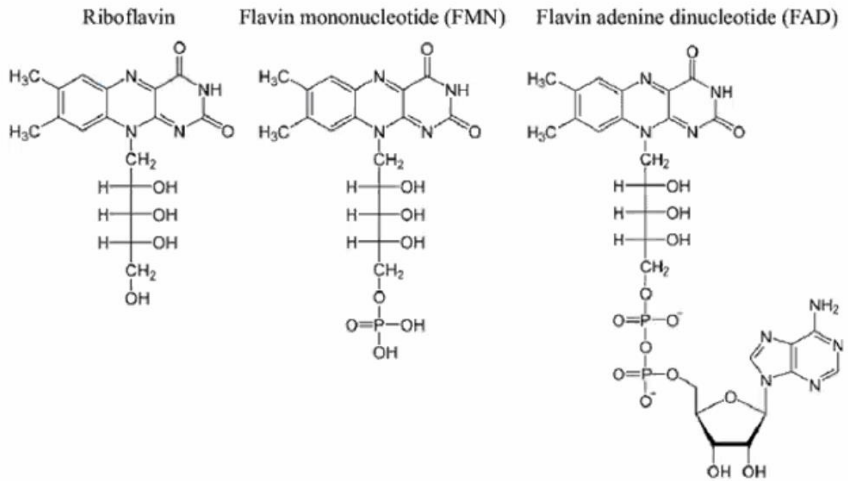
TABLE 2 Thiamine metabolism dysfunction syndromes nomenclature

Gene	Dysfunction syndrome	Disorder
SLC19A2	Thiamine metabolism dysfunction syndrome 1	Thiamine-responsive megaloblastic anemia syndrome
SLC19A3	Thiamine metabolism dysfunction syndrome 2	Biotin- or thiamine-responsive encephalopathy type
SLC25A19	Thiamine metabolism dysfunction syndrome 3	Microcephaly Amish type
	Thiamine metabolism dysfunction syndrome 4	Bilateral striatal degeneration and progressive polyneuropathy type
TPK1	Thiamine metabolism dysfunction syndrome 5	Episodic encephalopathy type

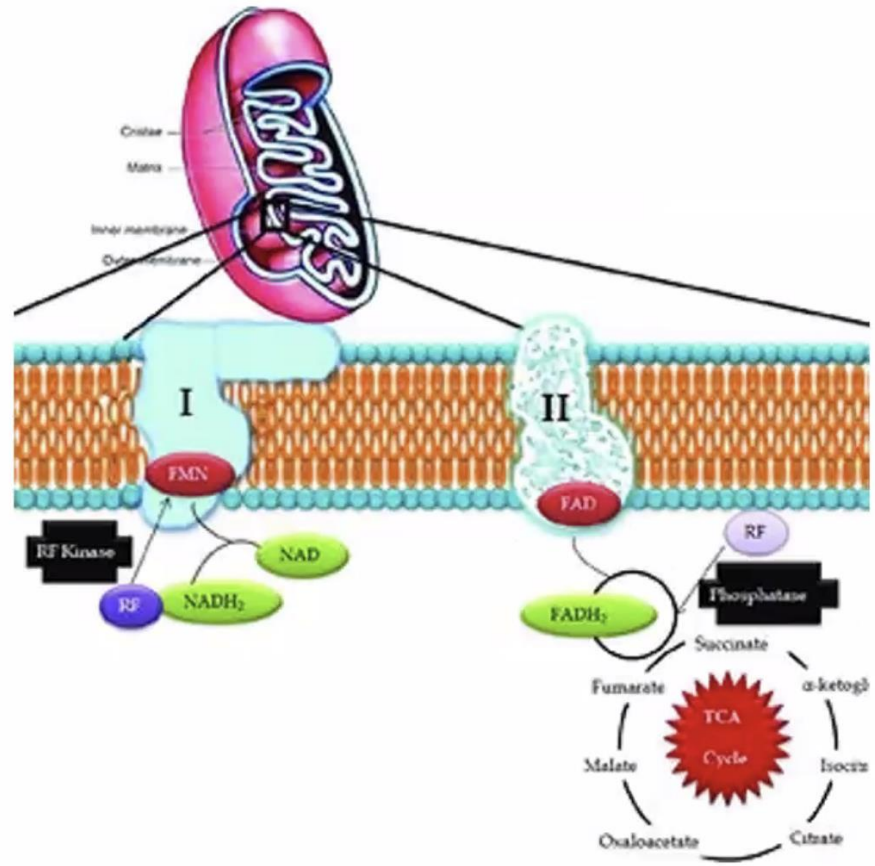
Cofactors

Riboflavin or Vitamin B2

- Riboflavin (Vitamin B2) is a precursor both of flavin mononucleotide(FMN), a necessary prosthetic component in the biosynthesis of respiratory chain complex I and flavin adenine dinucleotide (FADH2), the reducing equivalent consumed by respiratory chain complex II. Thus, vitamin B2 helps to promote the assembly of respiratory chain complex



Molecular masses: riboflavin: 376.4 g/mol; FMN: 456.3 g/mol, FAD: 785.6 g/mol.



Riboflavin dosage: 20 mg/kg/die
50-400 mg/die

Repp et al. Orphanet Journal of Rare Diseases (2018) 13:120
https://doi.org/10.1186/s13023-018-0784-8

Orphanet Journal of Rare Diseases

RESEARCH Open Access

Clinical, biochemical and genetic spectrum of 70 patients with ACAD9 deficiency: is riboflavin supplementation effective?

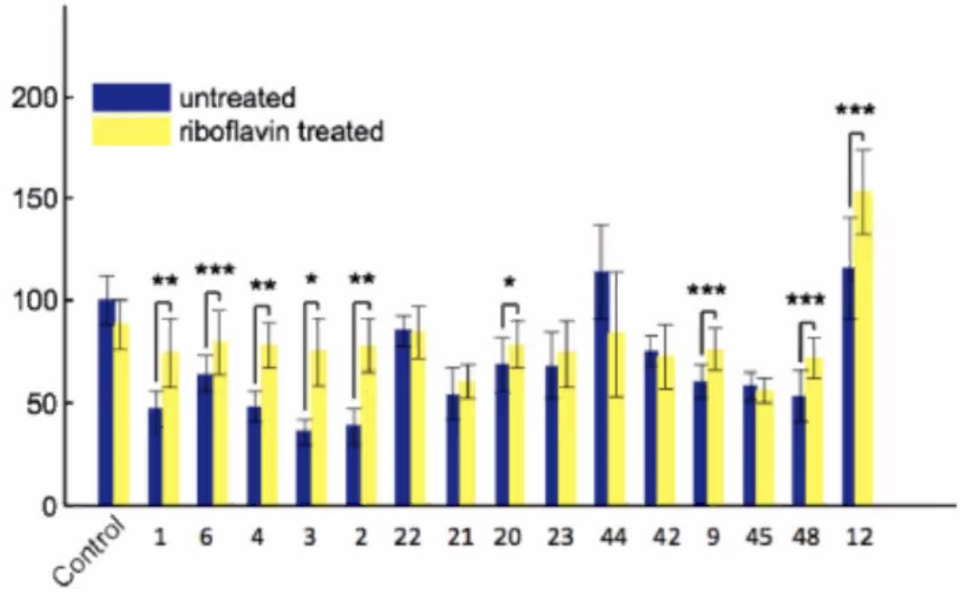
Birgit M. Repp[1,2], Elisa Mastantuono[1,2], Charlotte L. Alston[3], Manuel Schiff[4,5], Tobias B. Haack[1,46], Agnes Rötig[6], Anna Ardissone[7,8,9], Anne Lombès[10], Claudia B. Catarino[11], Daria Diodato[12], Gudrun Schottmann[13], Joanna Poulton[14], Alberto Burlina[15], An Jonckheere[16], Arnold Munnich[6], Boris Rolinski[17], Daniele Ghezzi[7,18], Dariusz Rokicki[19], Diana Wellesley[20], Diego Martinelli[21], Ding Wenhong[22], Eleonora Lamantea[7], Elsebet Ostergaard[23], Ewa Pronicka[19], Germaine Pierre[24], Hubert J. M. Smeets[25], Ilka Wittig[26], Ingrid Scurr[27], Irenaeus F. M. de Coo[28,29], Isabella Moroni[8], Joél Smet[30], Johannes A. Mayr[31], Lifang Dai[32], Linda de Meirleir[33,34], Markus Schuelke[13], Massimo Zeviani[35], Raphael J. Morscher[31,36], Robert McFarland[3], Sara Seneca[37], Thomas Klopstock[11,38,39], Thomas Meitinger[1,2,39,40], Thomas Wieland[2], Tim M. Strom[1,2], Ulrike Herberg[41], Uwe Ahting[1], Wolfgang Sperl[31], Marie-Cecile Nassogne[42], Han Ling[22], Fang Fang[32], Peter Freisinger[43], Rudy Van Coster[30], Valentina Strecker[26], Robert W. Taylor[3], Johannes Häberle[44], Jerry Vockley[45], Holger Prokisch[1,2] and Saskia Wortmann[1,2,31*]

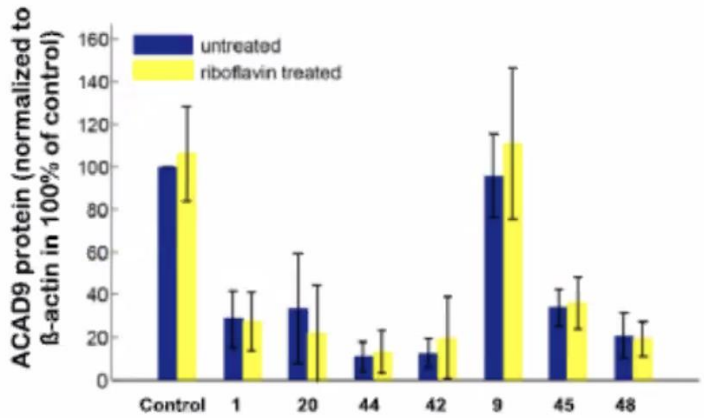
(Continued from previous page)

Conclusions: Our data show that riboflavin treatment improves complex I activity in the majority of patient-derived fibroblasts tested. This effect was also reported for most of the treated patients and is mirrored in the survival data. In the patient group with disease-onset below 1 year of age, we observed a statistically-significant better survival for patients treated with riboflavin.

Keywords: Complex I, Cardiomyopathy, Heart transplantation, Mitochondrial disorder, Lactic acidosis, Treatment, Prognosis, Neonatal, Vitamin, Activities of daily living

Maximal oxygen consumption rate (OCR)





Idebenone

LHON is at the forefront of mitochondrial diseases

first mitochondrial disease with an approved therapy (idebenone)


BRAIN

A randomized placebo-controlled trial of idebenone in Leber's hereditary optic neuropathy

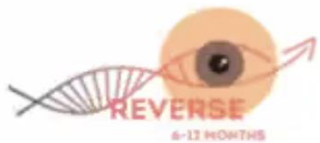

BRAIN

LETTER TO THE EDITOR

Idebenone treatment in Leber's Hereditary Optic Neuropathy


Real-World Clinical Experience With Idebenone in the Treatment of Leber Hereditary Optic Neuropathy

Clinical Trial	Natural History	Real-life data
RHODOS[1] ***n* = 85** Six month, double-blind, placebo-controlled RCT of idebenone in LHON patients aged 14-64 years 1 - 5 years onset	**Case Record Survey**[3] ***n* = 383** LHON natural history study with a large proportion of untreated patients	**EAP**[2] (Expanded Access Program) ***n* = 111** Real-world patient access program in 10 countries and 33 centers 1 year onset

Trial name/NCT number	Type/intervention	Primary endpoints	Secondary endpoints	Status/available results
Efficacy study of GS010 for the treatment of vision loss up to 6 months from onset in LHON due to t *NCT* 	**Interventional** **Phase III** Unilateral GS010 injection vs sham injection	Change from baseline in ETDRS VA at week 48	Number of eye and subject responders Change from baseline at week 72 and Week 96 in ETDRS VA Change from baseline at week 48, Week 72 and week 96 in: GCL Macular Volume RNFL temporal quadrant and papillomacular bundle thickness ETDRS total macular volume VF MD and foveal threshold Contrast sensitivity and colour vision	Completed Press release from the company stated improvement of BCVA from nadir, corresponding to 25 ETDRS letters equivalent, in GS010-treated eyes
Efficacy study of GS010 for treatment of vision loss from 7 months to 1 year from onset in LHON due to the ND4 mutation (REVERSE) *NCT02652780* 	**Interventional** **Phase III** Unilateral GS010 injection vs sham injection	Change from baseline in ETDRS VA at week 48	Number of eye and subject responders. Change from baseline at week 72 and Week 96 in ETDRS VA Change from baseline at week 48, 72 and 96 in: GCL macular volume RNFL temporal quadrant and papillomacular bundle thickness ETDRS total macular volume VF MD and foveal threshold Contrast sensitivity and colour vision	Completed Press release from the company stated improvement of BCVA from nadir, corresponding to 25 ETDRS letters equivalent, in GS010-treated eyes
RESCUE and REVERSE long-term follow-up (RESCUE/REVERSE) *NCT03406104*	**Interventional** **Phase III**	AEs or serious AEs (ocular or systemic) up to 5-year post-treatment	BCVA in logMAR, VF and OCT parameters, responder-eye analysis (improvement of at least 15 ETDRS letters/loss less than 15 ETDRS letters), time course of the response, visual improvement and quality of life measures up to 5-year post-treatment	Active, not recruiting Interim analysis on 15 recruited subjects showed a severe and usually irreversible decline in VA, in contrast with the improvement seen in REVERSE and RESCUE patients
Efficacy & safety study of bilateral IVT injection of GS010 in LHON subjects due to the ND4 mutation for up to 1 Year (REFLECT) *NCT03293524*	**Interventional** **Phase III** Bilateral intravitreal GS010 injection vs unilateral GS010 injection plus contralateral sham	BCVA in logMAR at 1-year post-treatment	BCVA at 2 years, responders* analysis, OCT and VF parameters, contrast sensitivity, quality of life measures at 1.5 and 2 years	Active, not recruiting Results unavailable

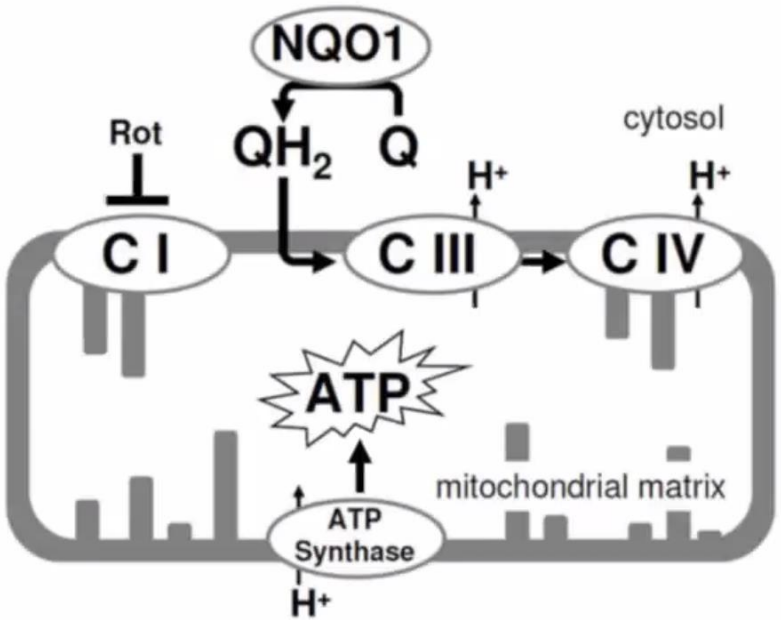
International Consensus Statement on the Clinical and Therapeutic Management of Leber's Hereditary Optic Neuropathy

Valerio Carelli, MD, PhD, Michele Carbonelli, MD, Irenaeus F. de Coo, MD, PhD, Aki Kawasaki, MD, Thomas Klopstock, MD, Wolf A. Lagrèze, MD, Chiara La Morgia, MD, PhD, Nancy J. Newman, MD, Christophe Orssaud, MD, Jan Willem R. Pott, MD, PhD, Alfredo A. Sadun, MD, PhD, Judith van Everdingen, MD, Catherine Vignal-Clermont, MD, Marcela Votruba, MD, PhD, Patrick Yu-Wai-Man, MD, PhD, Piero Barboni, MD

Carelli et al: *J Neuro-Ophthalmol 2017*; 0: 1-11

- L' Idebenone deve essere iniziato il prima possibile al dosaggio di 900 mg al giorno in pazienti che hanno una durata di malattia inferiore ad 1 anno
- Non ci sono al momento sufficienti dati scientifici per raccomandare l'utilizzo di Raxone in pazienti cronici
- La terapia deve essere proseguita per almeno 1 anno e fino a quando non si raggiunge la stabilita in 2 controlli semestrali consecutivi (plateau)

It has extensively been demonstrated that in the presence of CoQ10, Idebenone activates alternative pathways to circumvent dysfunctional complex I.



- The best known of these pathways is mediated by the cytoplasmic enzyme NADH-quinone oxidoreductase 1 (NQO1).
- This enzyme reduces Idebenone upon entering the cell as part of a response to detoxify quinones and prevent ROS production.
- Then, the reduced Idebenone enters mitochondria, where it is directly oxidized by complex III. By donating electrons from the cytoplasm to complex III, Idebenone successfully negotiates complex I to complex III electron transport.
- In light of this evidence, it would be reasonable to prioritize the application of Idebenone-based therapies rather than CoQ10 treatments on patients of complex I-related diseases such as Leigh syndrome.

Antioxidants **2021**, *10*, 236. https://doi.org/10.3390/antiox10020236

FARMACI E MALATTIE MITOCONDRIALI

Received: 8 October 2019 | Revised: 18 November 2019 | Accepted: 19 November 2019

DOI: 10.1002/jimd.12196

Check for updates

ORIGINAL ARTICLE

JIMD SSIEM WILEY

Safety of drug use in patients with a primary mitochondrial disease: An international Delphi-based consensus

Maaike C. De Vries[1] | David A. Brown[2] | Mitchell E. Allen[2] | Laurence Bindoff[3,4] | Gráinne S. Gorman[5,6] | Amel Karaa[7] | Nandaki Keshavan[8,9] | Costanza Lamperti[10] | Robert McFarland[5,6] | Yi Shiau Ng[5,6] | Mar O'Callaghan[11,12] | Robert D. S. Pitceathly[13] | Shamima Rahman[8,9] | Frans G. M. Russel[14] | Kristin N. Varhaug[3,4] | Tom J. J. Schirris[14] | Michelangelo Mancuso[15]

Conclusioni workshop

Curare le comorbidità intercorrenti con i farmaci appropriati

I singoli individui possono rispondere in modo diverso ai farmaci e che gli effetti collaterali possono verificarsi in chiunque e non sono necessariamente correlati alla malattia mitocondriale primaria

La buona pratica clinica tra cui indicazioni generali, controindicazioni, il monitoraggio clinico e gli effetti collaterali per tutti i farmaci devono sempre essere tenuti a mente (p. mitocondriale oppure no)

Monitorare la risposta al farmaco sia in termini di efficacia che di sicurezza (laddove richiesto esami ematici –lattato e CPK per esempio- e\o strumentali)

Conclusioni workshop II

Tutti i farmaci in cui sono le prove in vivo di tossicità mitocondriale sono assenti o scarse, possono essere utilizzati con un attento monitoraggio nei primi giorni di trattamento per potenziali effetti collaterali, e se necessario attraverso la misurazione di lattato di sangue

Come approccio generale, il trattamento antibiotico a breve termine (<7 giorni) è improbabile che causi un problema serio nei pazienti mitocondriali. L'infezione è un rischio molto maggiore di quello collegabile alla assunzione di antibiotici a breve termine

Evitare assunzione di aminoglucosidi in presenza di mutazioni nel DNA mitocondriale a rischio (es. m.1555A > G and m.1494C > T)

Cautela con linezolid

Conclusioni workshop III

- Acido valproico (Depakin…).
  - Controindicato assolutamente nei pazienti con mutazione POLG
  - In pazienti non-POLG e con funzione epatica normale, l'acido valproico potrebbe essere usato per gestire l'epilessia refrattaria e disturbi dell'umore refrattari (quindi mai come prima scelta ma se necessario si può utilizzare in questi p)

Conclusioni workshop IV: anestesia

- Bloccanti neuromuscolari in anestesia
  - È necessario prestare particolare attenzione e monitoraggio ai pazienti che manifestano prevalentemente fenotipo miopatico.
- Propofol si può utilizzare per indurre anestesia
- Midazolam sicuro
- Il catabolismo dovrebbe essere prevenuto minimizzando il digiuno e la somministrazione preoperatoria glucosio per via endovenosa durante l'intervento per anestesia prolungata

PMD Recommendations

Patient care standards for primary mitochondrial disease:

a consensus statement from the Mitochondrial Medicine Society.

The purpose of this statement is to provide consensus-based recommendations for optimal management and care for patients with primary mitochondrial disease. This statement is intended for physicians who are engaged in the diagnosis and management of these patients.

Parikh S et al. Genet Med. 2017 Dec;19(12).

Diagnosis and management of mitochondrial disease:

a consensus statement from the Mitochondrial Medicine Society.

The purpose of this statement is to review the literature regarding mitochondrial disease and to provide recommendations for optimal diagnosis and treatment. This statement is intended for physicians who are engaged in diagnosing and treating these patients.

Parikh S et al. Genet Med. 2015 Sep;17(9):689-701.

NORD GUIDE PMM: https://rarediseases.org/physician-guide/mitochondrial-myopathy/

PMD Recommendations II

Wellcome Open Research

Wellcome Open Research 2019, 4:201 Last updated: 11 FEB 2020

Check for updates

RESEARCH ARTICLE

Consensus-based statements for the management of mitochondrial stroke-like episodes [version 1; peer review: 2 approved]

Yi Shiau Ng [1-3], Laurence A. Bindoff[4,5], Gráinne S. Gorman[1-3], Rita Horvath[1,6], Thomas Klopstock[7-9], Michelangelo Mancuso [10], Mika H. Martikainen [11], Robert Mcfarland [1,3,12], Victoria Nesbitt[13,14], Robert D. S. Pitceathly [15,16], Andrew M. Schaefer[1-3], Doug M. Turnbull[1-3]

EAN GUIDELINES/CME ARTICLE

Monogenic cerebral small-vessel diseases: diagnosis and therapy. Consensus recommendations of the European Academy of Neurology

M. Mancuso[a], M. Arnold[b], A. Bersano[c], A. Burlina[d], H. Chabriat[e], S. Debette[f], C. Enzinger[g], A. Federico[h], A. Filla[i], J. Finsterer[j], D. Hunt[k], S. Lesnik Oberstein[l], E. Tournier-Lasserve[m] and H. S. Markus[n]

MELAS MANAGEMENT

- Fibrinolysis is not indicated to treat SLE
- Antiplatelet therapies are not indicated for secondary prevention of SLEs
- If an SLE is suspected and focal seizures are evident, they should be treated urgently with intravenous antiepileptic drugs, including levetiracetam, benzodiazepines or lacosamide.
- Valproic acid is contraindicated, mainly in patients with POLG variants
- We recommend midazolam as the first choice of general anaesthetics agent for treating refractory status epilepticus associated with SLE
- There is not enough evidence to support the use of intravenous L-arginine or citrulline to treat SLEs
- Even though there is no scientific evidence of positive impact of steroids in SLEs, their use is not contraindicated

Ng et al, 2020
Mancuso et al, 2020

MELAS MANAGEMENT- II

- Drugs like haloperidol, benzodiazepine, quetiapine, olanzapine may be safely used to treat psychiatric complications in MELAS
- Because of the frequent occurrence of arrhythmia in MELAS (especially if caused by m.3243A>G), electrocardiogram monitoring during an SLE, especially after the introduction of an antipsychotic drug with QT interval monitoring should be considered
- Fluid management, nutrition and gut dysmotility
- Management of lactic acidaemia: often respond well to rehydration. A buffering agent such as sodium bicarbonate can be used with care in severe lactic acidosis (pH <7.1)

Ng et al, 2020
Mancuso et al, 2020

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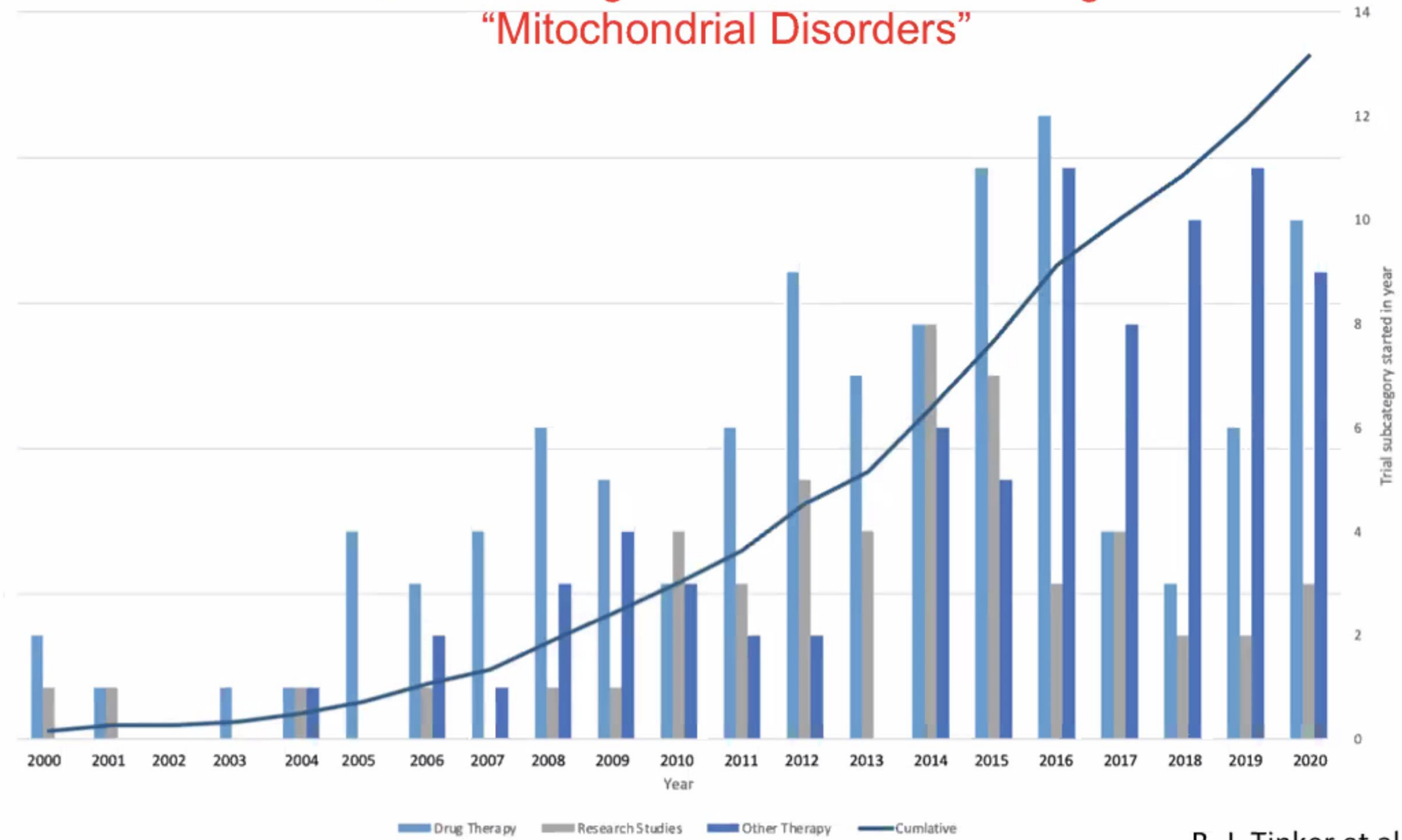
https://www.mitocon.it/guida-gestione-emergenze/

SPERIMENTAZIONI

Clinical trials registered at ClinicalTrials.gov
"Mitochondrial Disorders"



R. J. Tinker et al. 2021

TRIAL READYNESS!!!

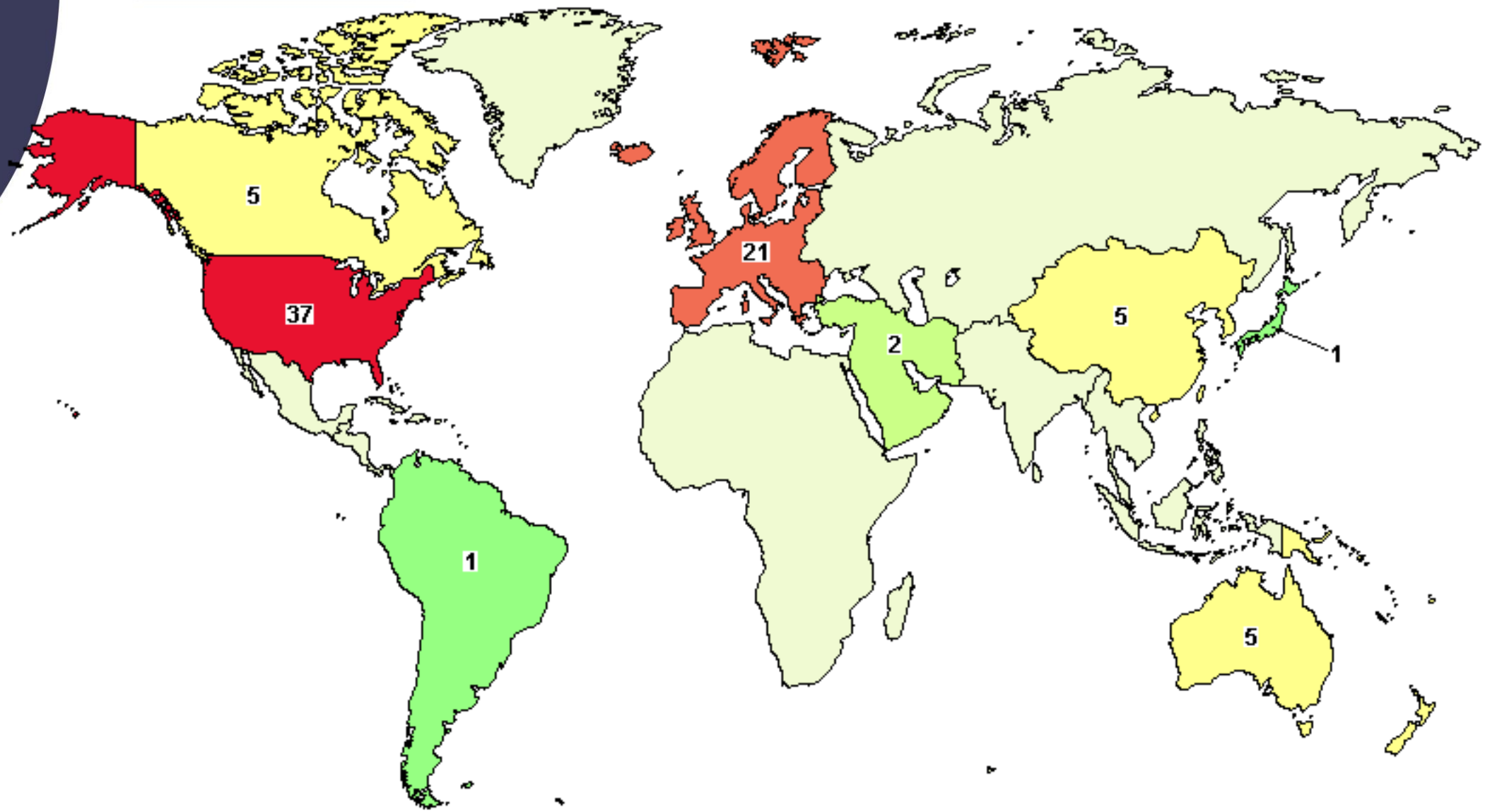
April 13, 2022

MITOCHONDRIAL DISEASES: 289

MITOCHONDRIAL DISEASES COMPLETED : 117

MITOCHONDRIAL DISEASES RECRUITING OR READY TO RECRUIT: 107
INTERVENTIONAL STUDIES 65(active and\or recruiting)

https://clinicaltrials.gov/ct2/results?cond=Mitochondrial+Diseases&term=&cntry=&state=&city=&dist=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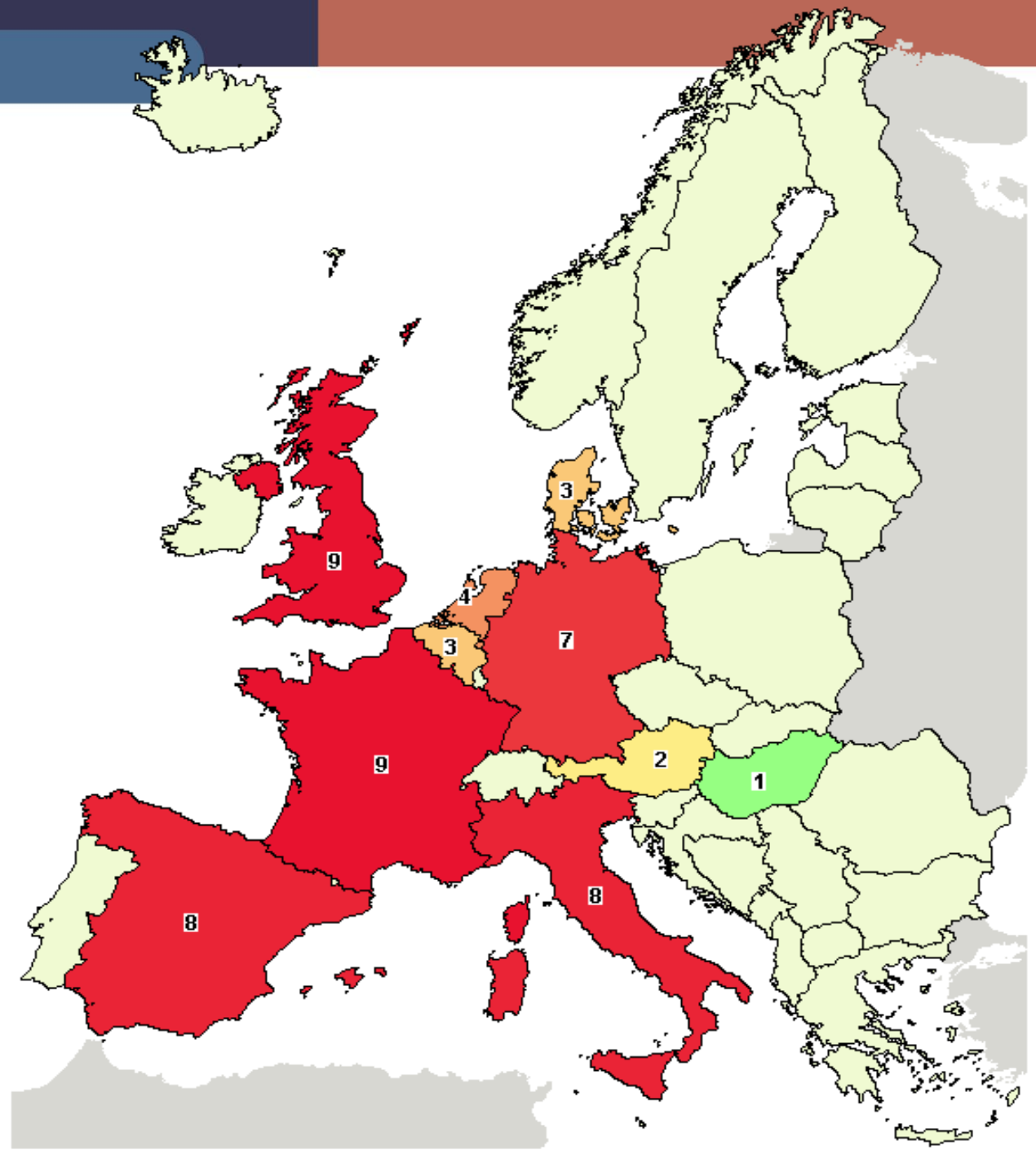
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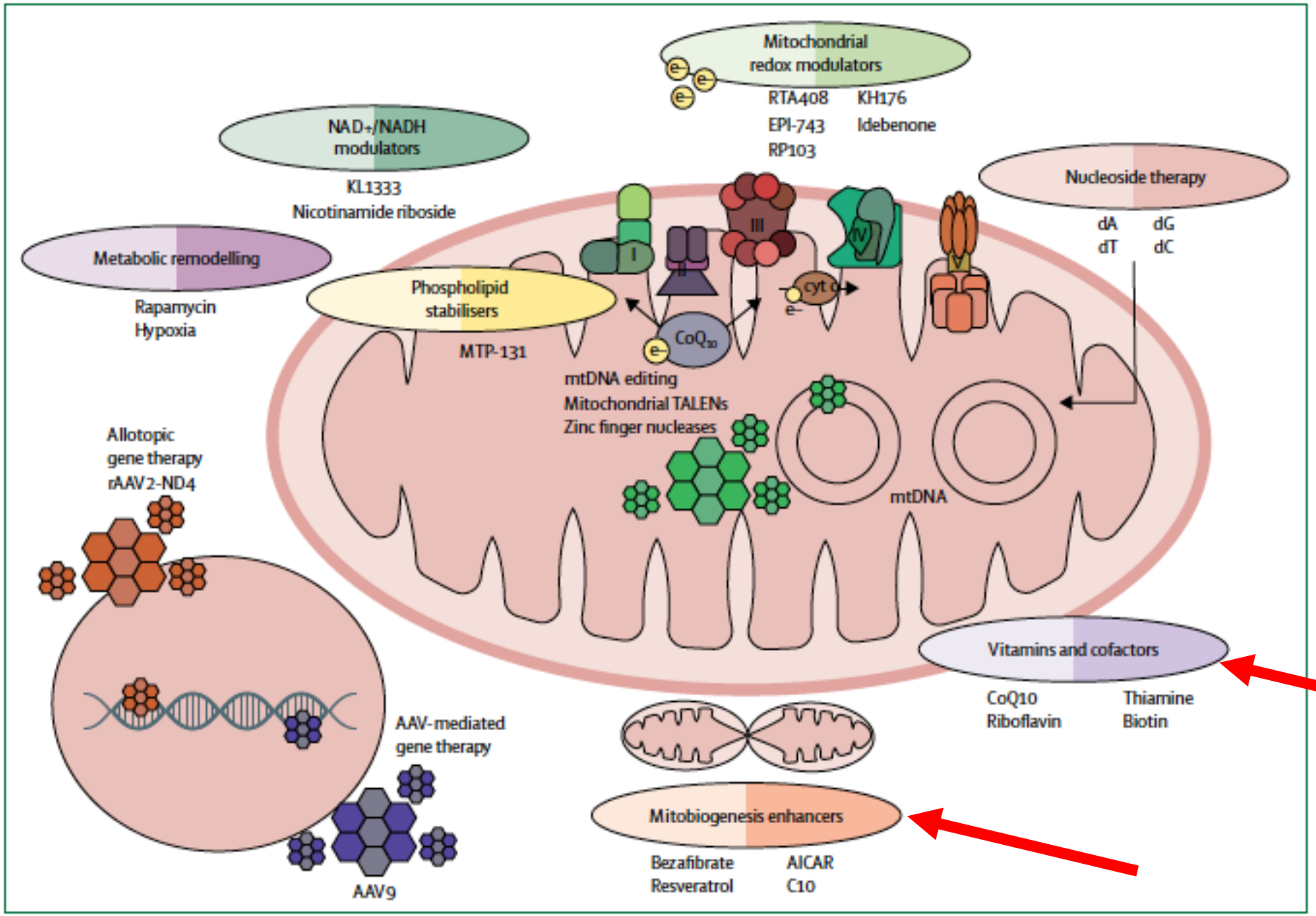


Figure 3: **Mitochondrial therapies in development**

Despite the absence of approved curative therapies for mitochondrial disease, several pharmacological and genetic approaches to ameliorating the pathology of mitochondrial disease are under investigation. mtDNA=mitochondrial DNA.

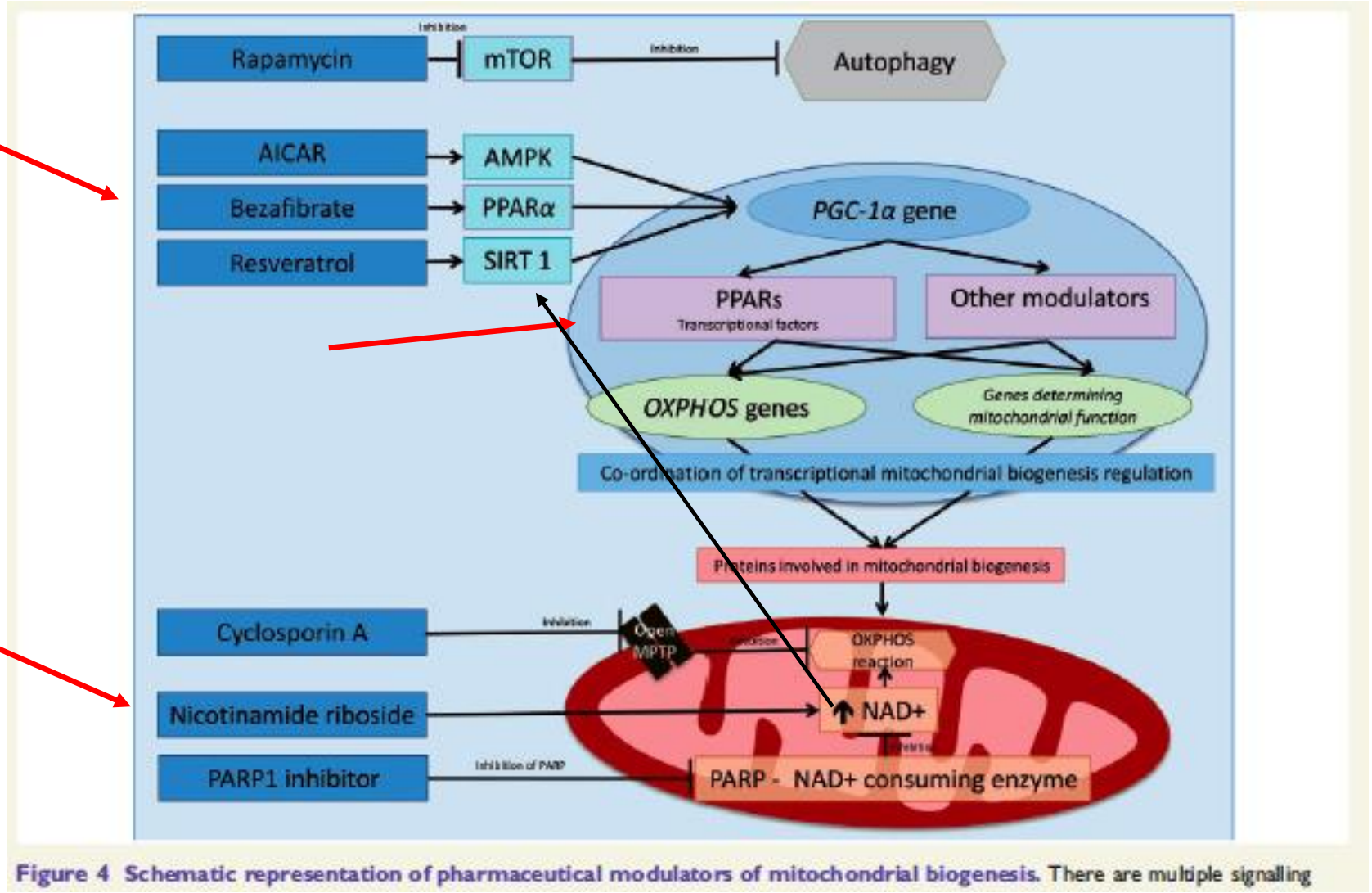


Figure 4 Schematic representation of pharmaceutical modulators of mitochondrial biogenesis. There are multiple signalling

Report

TRANSPARENT PROCESS OPEN ACCESS

EMBO Molecular Medicine

Metabolic effects of bezafibrate in mitochondrial disease

Hannah Steele[1,†], Aurora Gomez-Duran[2,3,†], Angela Pyle[1,4], Sila Hopton[4,5], Jane Newman[4,6], Renae J Stefanetti[6], Sarah J Charman[7], Jehill D Parikh[7], Langping He[4,5], Carlo Viscomi[3], Djordje G Jakovljevic[7], Kieren G Hollingsworth[7], Alan J Robinson[3], Robert W Taylor[4,5,6], Leonardo Bottolo[8,9,10,‡], Rita Horvath[2,‡] & Patrick F Chinnery[2,3,‡,*]

6 m.3243 PMM

Research Article

TRANSPARENT PROCESS SOURCE DATA OPEN ACCESS

EMBO Molecular Medicine

Effective trea nicotinamide

Nahid A Khan[1], Mari Aura
Lotta Pasila[1], Vidya Velaga

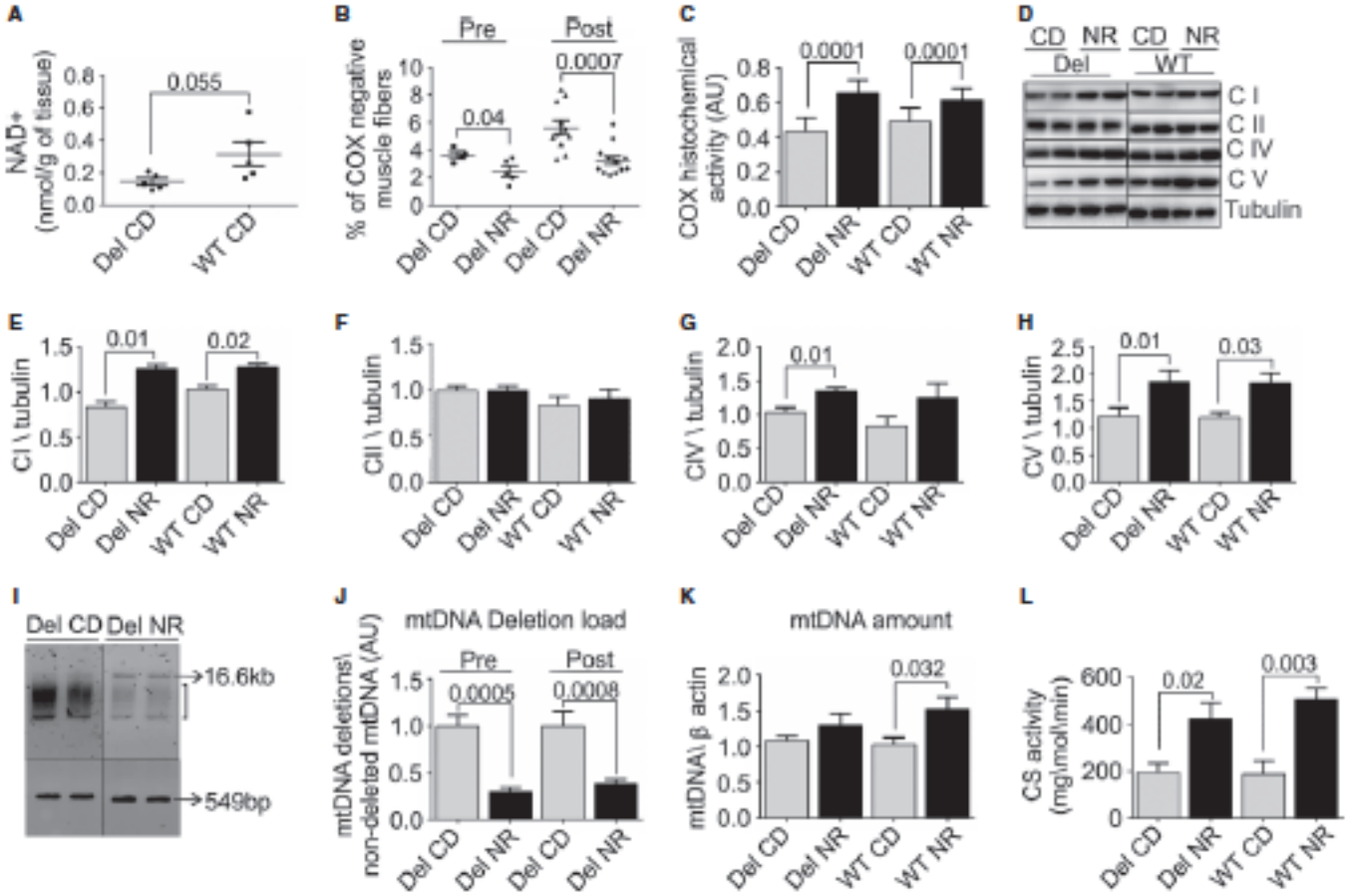


Figure 1. Nicotinamide riboside (NR) induces mitochondrial biogenesis and effectively ameliorates morphological and genetic landmarks of mitochondrial myopathy.

A Skeletal muscle NAD^+ content in 23- to 27-month-old Deletors and WT mice ($n = 5$ in each group).

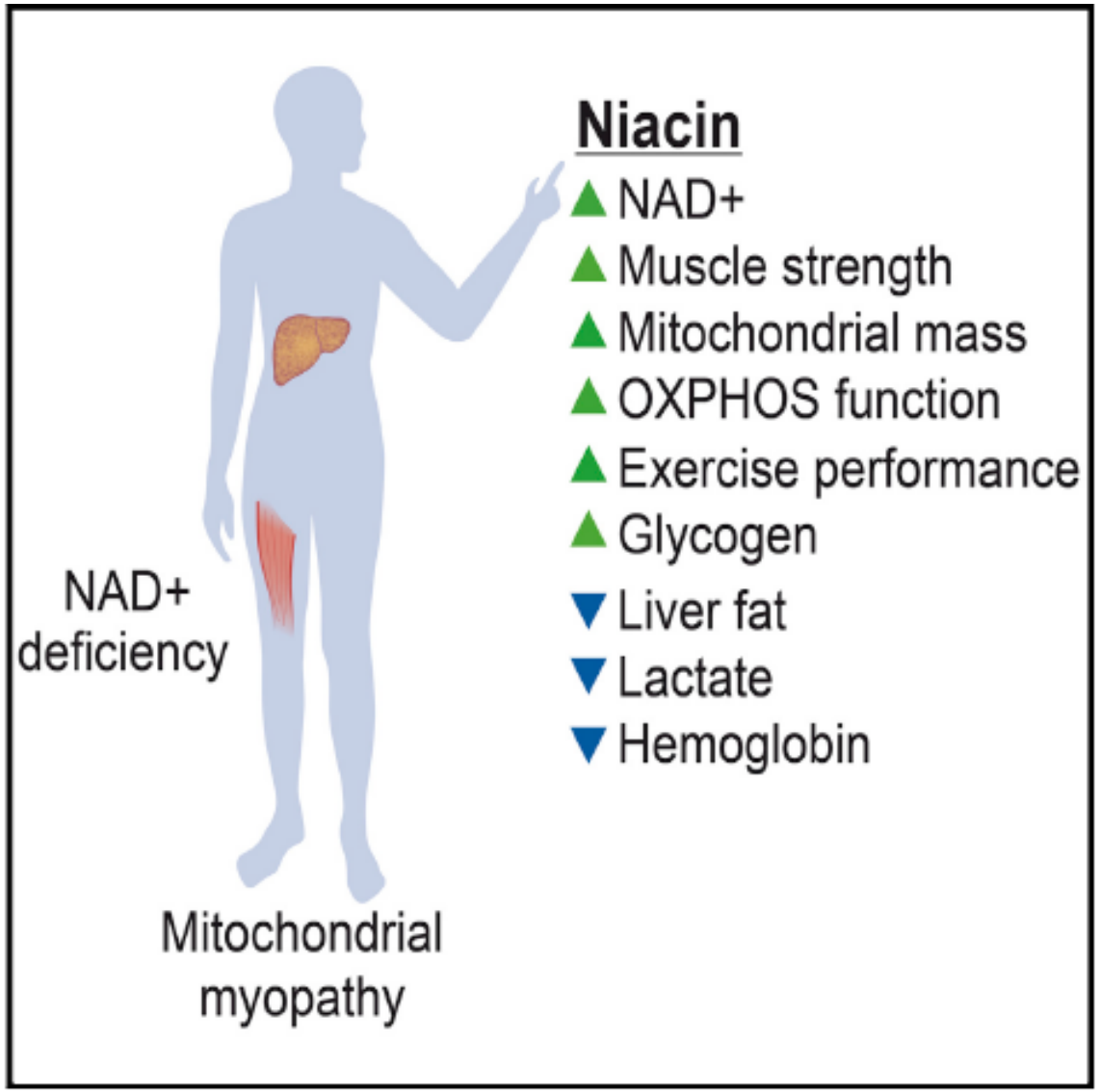
B Quantification of muscle fibers showing decreased COX activity in histochemical analysis of frozen sections of *quadriceps femoris* muscle (total fibers $n = 2000$

In Brief

Pirinen et al. report that niacin, a vitamin B3, can efficiently rescue NAD^+ levels in the muscle and blood of patients with mitochondrial myopathy, improving disease signs and muscle strength. NAD^+ levels increased also in healthy subjects. The evidence suggests that niacin is an effective NAD^+ booster in humans.

Cell Metabolism Clinical and Translational Report

Niacin Cures Systemic NAD^+ Deficiency and Improves Muscle Performance in Adult-Onset Mitochondrial Myopathy

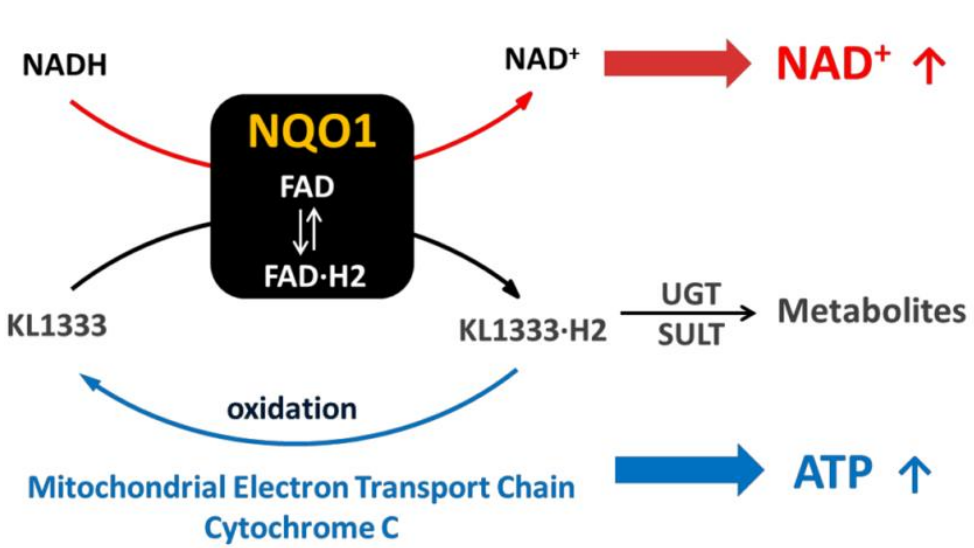


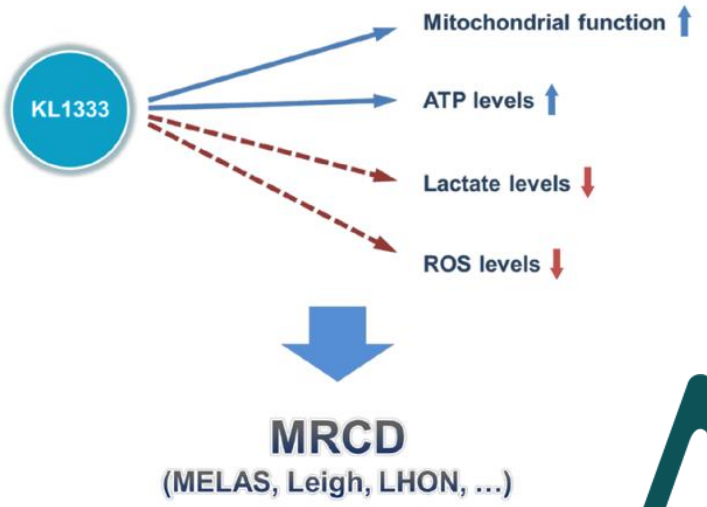
REN001 in Patients With mtDNA PMM

PPAR agonist
FDA ORPHAN DRUG DESIGNATION
Phase 1 OK

Phase 2b. Randomized, double-blind, placebo-controlled, parallel group, multi-centre, study designed to investigate the efficacy and safety of REN001 administered once daily over a 24-week period to patients with PMM.
NOW RUNNING (Italy: Pisa, Messina, Besta, Rome)

A Phase Ia/Ib, SAD and MAD Study of of KL1333 in Healthy Subjects and Patients With Primary Mitochondrial Disease, just closed in UK





ABLIVA

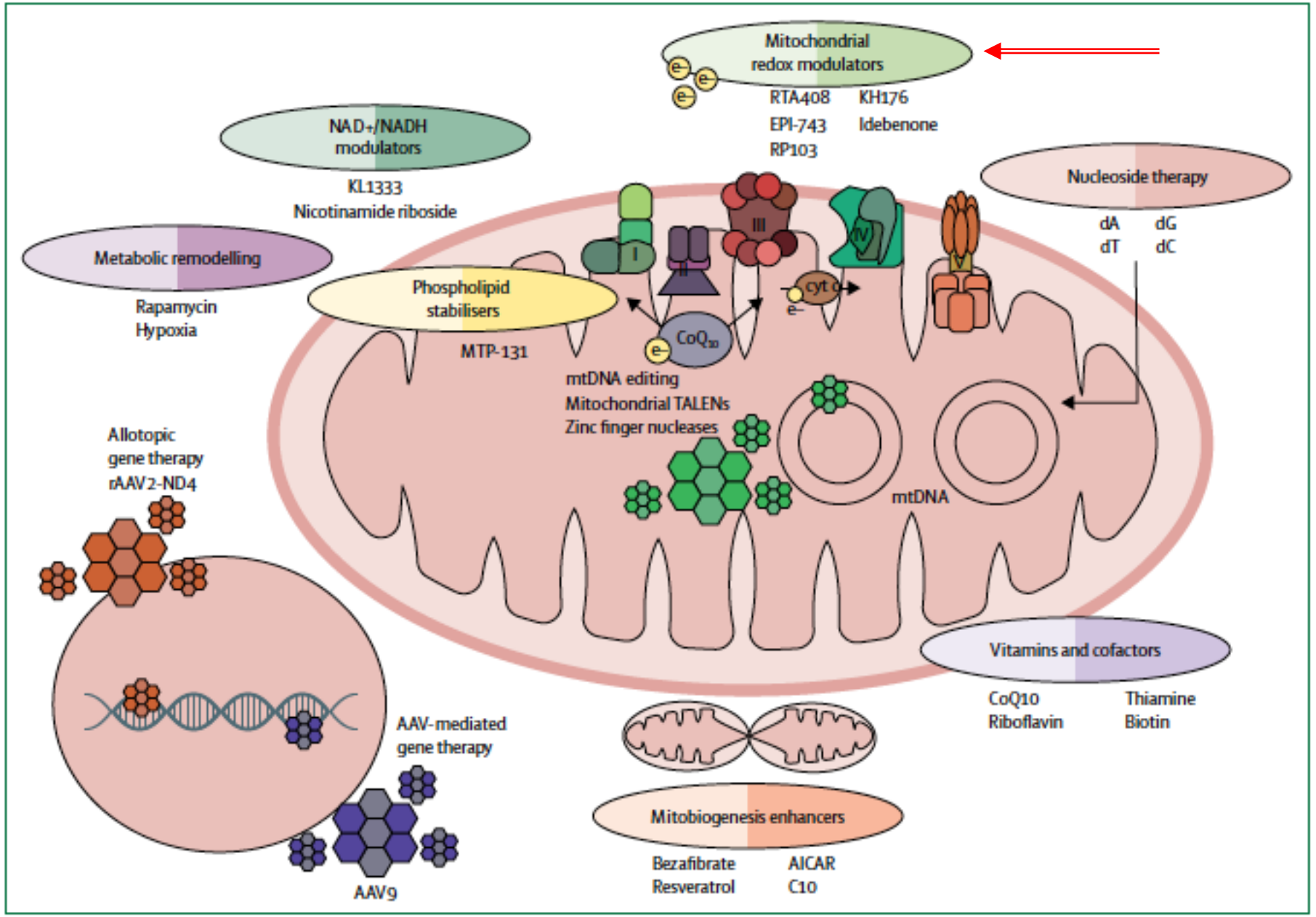


Figure 3: **Mitochondrial therapies in development**

Despite the absence of approved curative therapies for mitochondrial disease, several pharmacological and genetic approaches to ameliorating the pathology of mitochondrial disease are under investigation. mtDNA=mitochondrial DNA.

Koene et al. Orphanet Journal of Rare Diseases (2017) 12:163
DOI 10.1186/s13023-017-0715-0

Orphanet Journal of Rare Diseases

RESEARCH Open Access

KH176 under development for rare mitochondrial disease: a first in man randomized controlled clinical trial in healthy male volunteers

Saskia Koene[1], Edwin Spaans[2], Luc Van Bortel[3], Griet Van Lancker[3], Brant Delafontaine[3], Fabio Badilini[4], Julien Beyrath[2] and Jan Smeitink[1,2*]

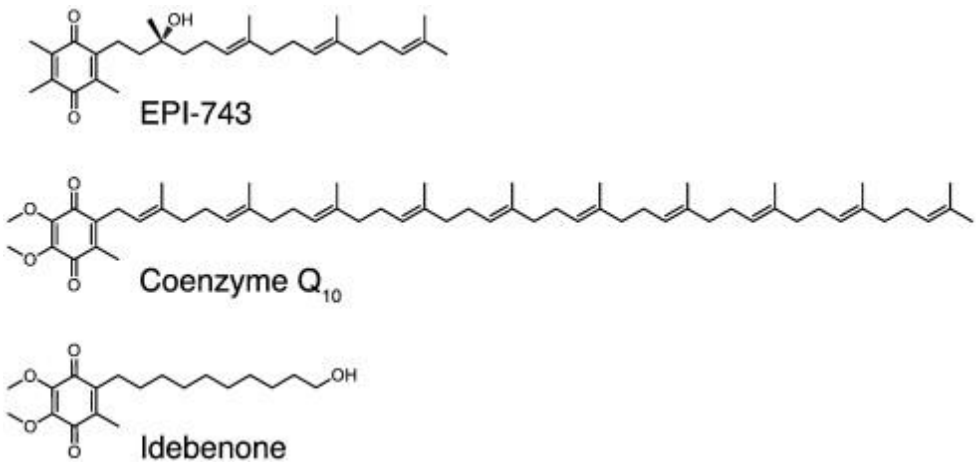
- KH176 is well tolerated up to single doses of 800 mg and multiple doses of 400 mg b.i.d
- Only at high doses, KH176 causes clinically relevant changes in cardiac electrophysiology, including prolonged QTc interval and changes in T wave morphology.

The KHENERGY Study: Safety and Efficacy of KH176 in Mitochondrial m.3243A>G Spectrum Disorders

Mirian C.H. Janssen[1,2], Saskia Koene[1], Paul de Laat[1], Pleun Hemelaar[3], Peter Pickkers[3], Edwin Spaans[4], Rypko Beukema[5], Julien Beyrath[4], Jan Groothuis[6], Chris Verhaak[7] and Jan Smeitink[4]

- Twice daily oral 100 mg KH176 was well tolerated and safe.
- No serious treatment-emergent adverse events were reported.
- No significant improvements in gait parameters or other outcome measures were obtained, except for a positive effect on alertness and mood, although a coincidence due to multiplicity cannot be ignored.

A Study to Evaluate Efficacy and Safety of Vatiquinone for Treating Mitochondrial Disease in Participants With Refractory Epilepsy



Molecular Genetics and Metabolism 107 (2012) 383–388

Contents lists available at SciVerse ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme

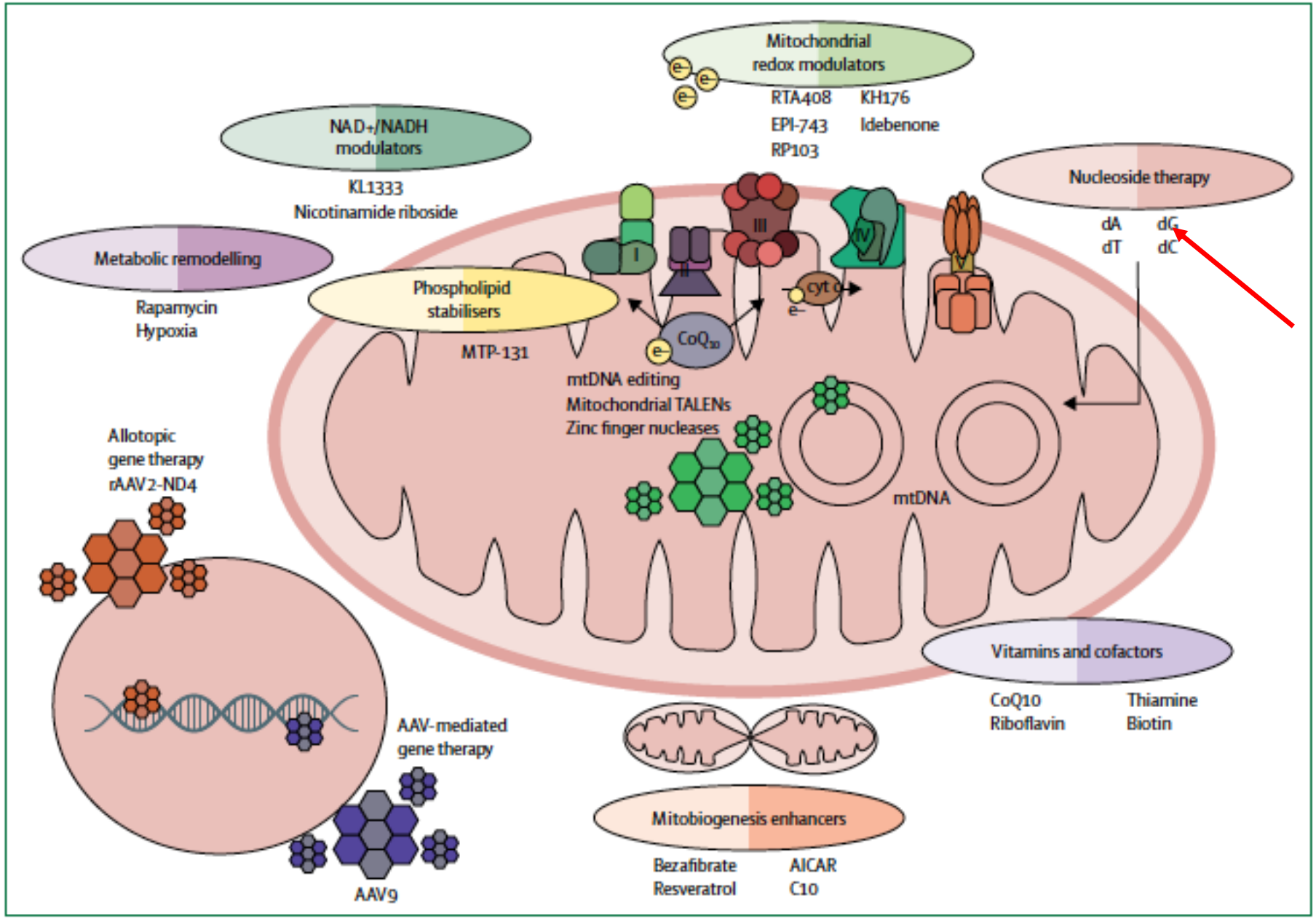
EPI-743 reverses the progression of the pediatric mitochondrial disease—Genetically defined Leigh Syndrome

Diego Martinelli [a], Michela Catteruccia [b], Fiorella Piemonte [b], Anna Pastore [a], Giulia Tozzi [b], Carlo Dionisi-Vici [a], Giuseppe Pontrelli [c], Tiziana Corsetti [d], Susanna Livadiotti [c], Viktoria Kheifets [e], Andrew Hinman [e], William D. Shrader [e], Martin Thoolen [e], Matthew B. Klein [e], Enrico Bertini [b], Guy Miller [e,f,*]

[a] *Bambino Gesù Children's Hospital, IRCCS; Division of Metabolism, Piazza S. Onofrio, 4, 00165 Rome, Italy*
[b] *Unit of Neuromuscular and Neurodegenerative Disorders, Piazza S. Onofrio, 4, 00165 Rome, Italy*
[c] *Clinical Trial Center, Piazza S. Onofrio, 4, 00165 Rome, Italy*
[d] *Central Pharmacy, Piazza S. Onofrio, 4, 00165 Rome, Italy*
[e] *Edison Pharmaceuticals, 350 North Bernardo Avenue, Mountain View, CA 94043, USA*
[f] *Adjunct Clinical Instructor, Department of Anesthesiology, Critical Care Medicine, Stanford University, Stanford, CA 94305, USA*

Running

Phase III double-blind, 9 months, randomised, placebo-controlled, multi-center parallel design study to evaluate the efficacy and long-term safety of Sonlicromanol in subjects with a genetically confirmed mitochondrial DNA tRNALeu(UUR) m.3243A>G mutation followed by an open-label extension study



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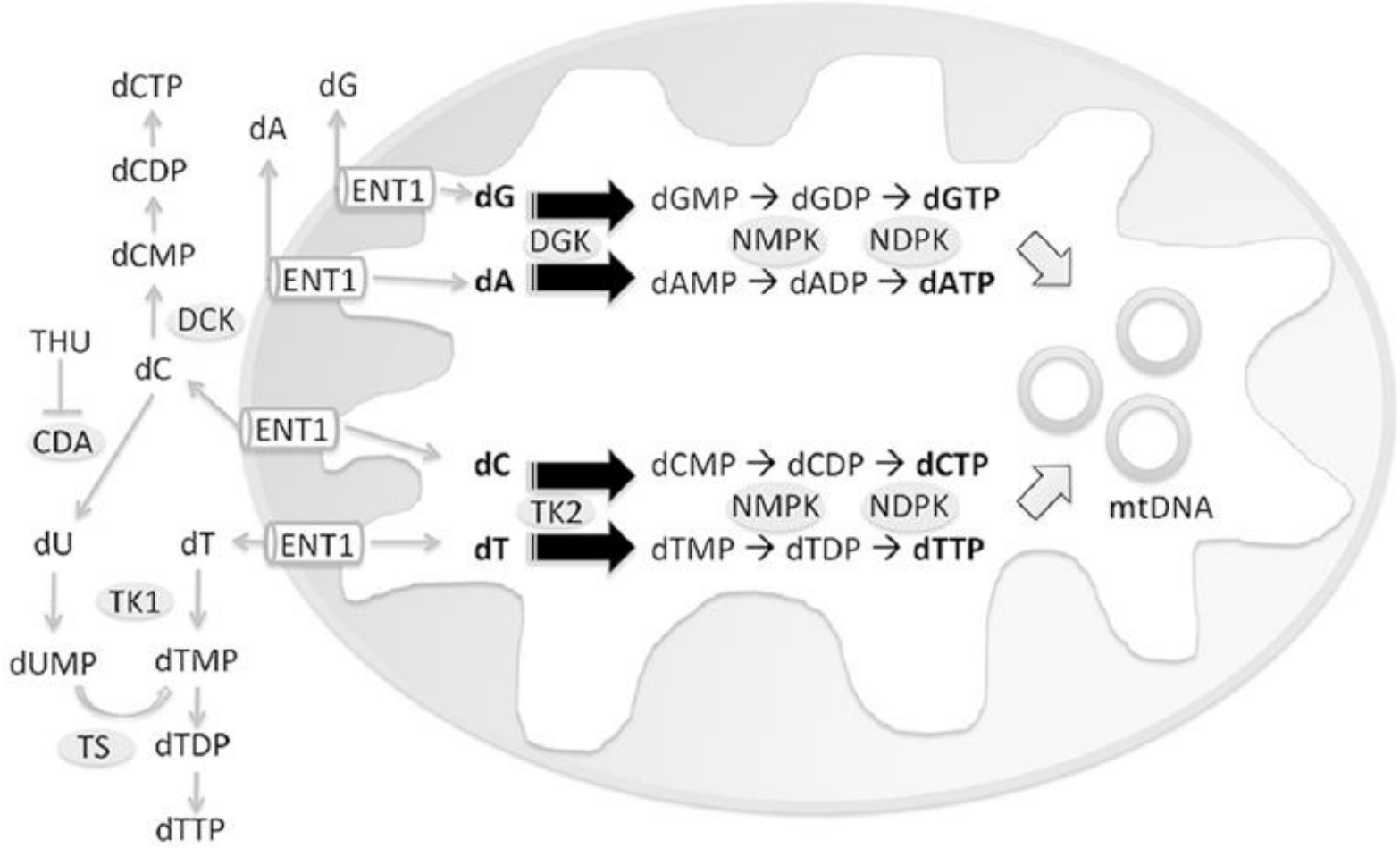
Despite the absence of approved curative therapies for mitochondrial disease, several pharmacological and genetic approaches to ameliorating the pathology of mitochondrial disease are under investigation. mtDNA=mitochondrial DNA.

Deoxynucleoside/deoxynucleotide for TK2 deficiency



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

10 May 2017
EMA/210409/2017
Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

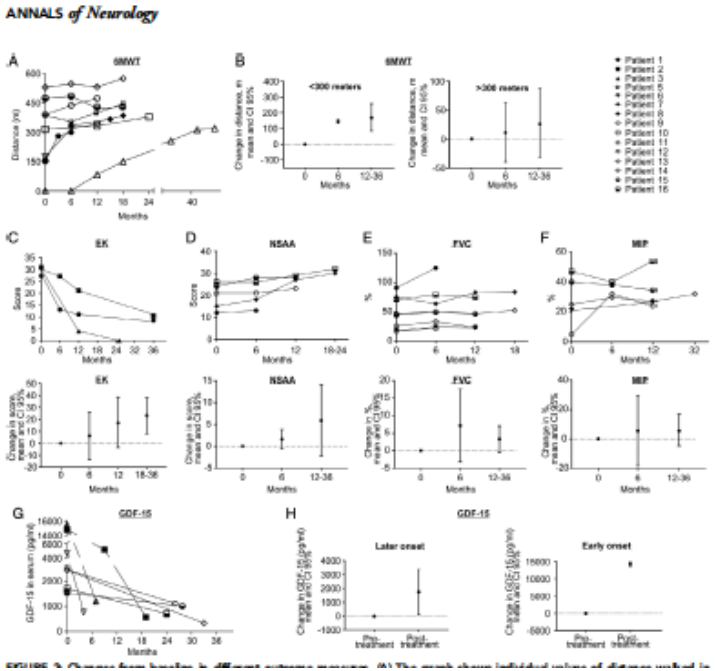
Thymidine and deoxycytidine for treatment of mitochondrial DNA depletion syndrome, myopathic form

On 20 April 2017, orphan designation (EU/3/17/1870) was granted by the European Commission to Vall d'Hebron Institute of Research, Spain, for thymidine and deoxycytidine for treatment of mitochondrial DNA depletion syndrome, myopathic form.

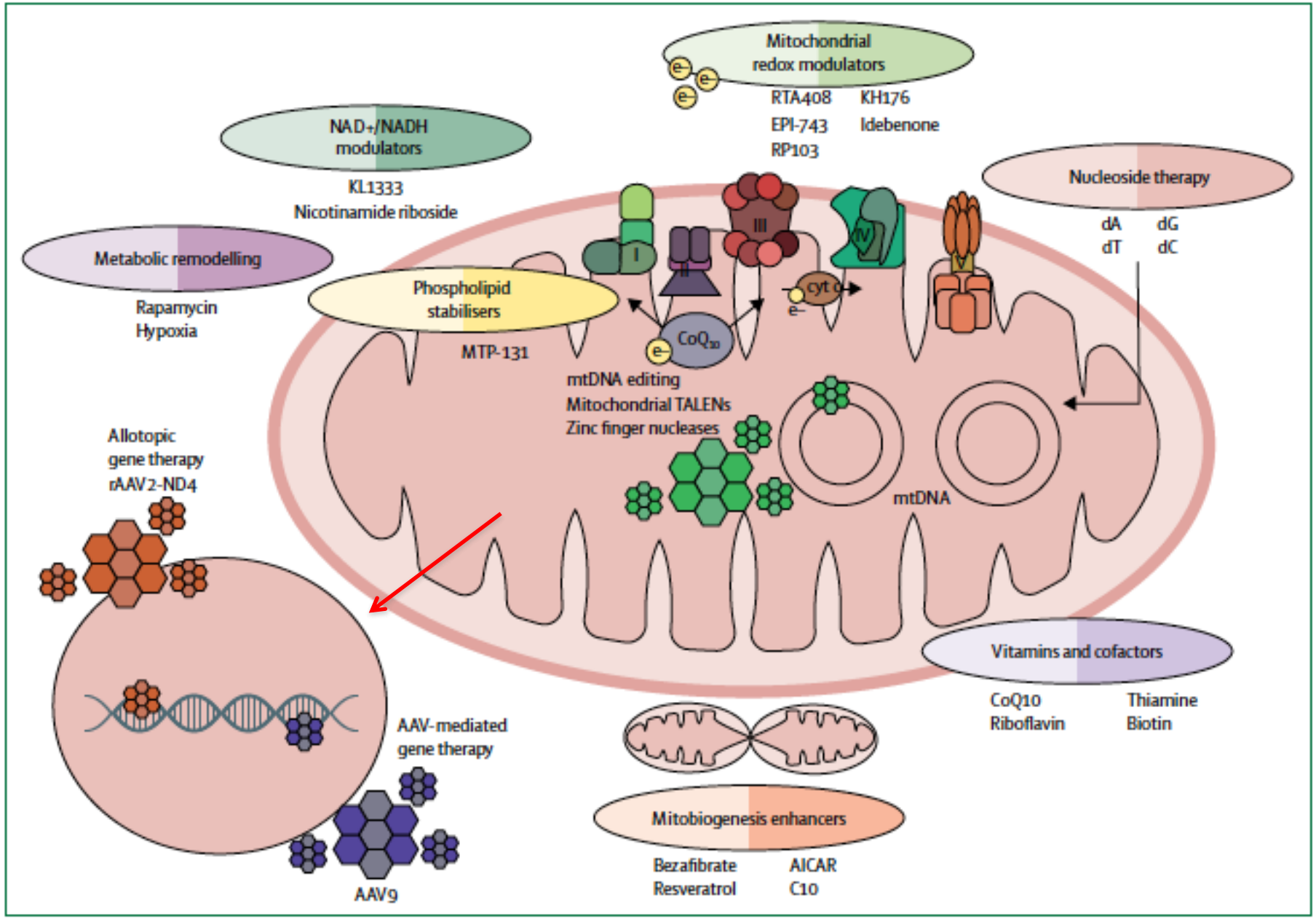
Deoxynucleoside Therapy for Thymidine Kinase 2–Deficient Myopathy

Cristina Domínguez-González, MD,[1,2,3] Marcos Madruga-Garrido, MD,[4] Fabiola Mavillard, PhD,[5,6] Caterina Garone, MD, PhD,[7] Francisco Javier Aguirre-Rodríguez, MD,[8] M. Alice Donati, MD,[9] Karin Kleinsteuber, MD,[10] Itxaso Martí, MD,[11] Elena Martín-Hernández, MD,[2,3,12] Juan P. Morealejo-Aycinena, MD,[13] Francina Munell, MD,[14] Andrés Nascimento, MD,[3,15] Susana G. Kalko, PhD,[3,15] M. Dolores Sardina, MD,[16] Concepcion Álvarez del Vayo, MD,[6,17] Olga Serrano, MD,[18] Yuelin Long, BS,[19] Yuqi Tu, BS,[19] Bruce Levin, PhD,[19] John L. P. Thompson, PhD,[19] Kristen Engelstad, MS,[20] Jasim Uddin, BS,[20] Javier Torres-Torronteras, PhD,[3,21] Cecilia Jimenez-Mallebrera, PhD,[3,15] Ramon M Carmen Paradas, MD, PhD,[5,6] and Michio Hira

16 TK2 cases



ZOGENIX



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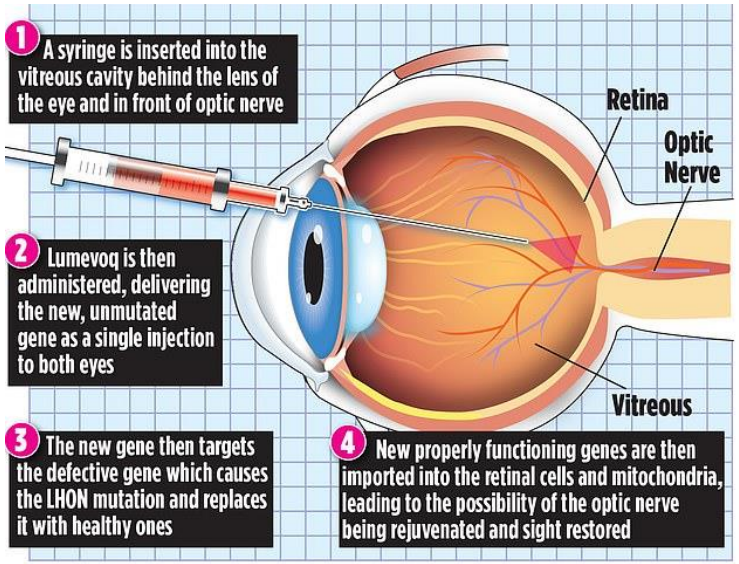
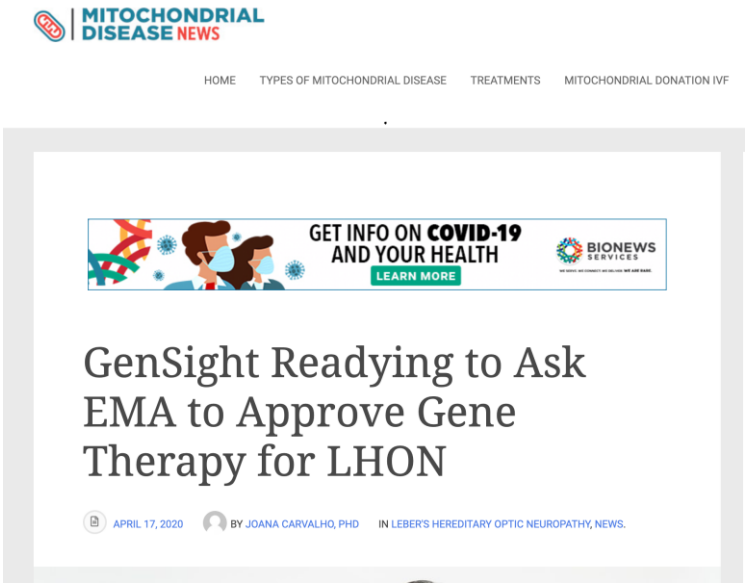
Despite the absence of approved curative therapies for mitochondrial disease, several pharmacological and genetic approaches to ameliorating the pathology of mitochondrial disease are under investigation. mtDNA=mitochondrial DNA.





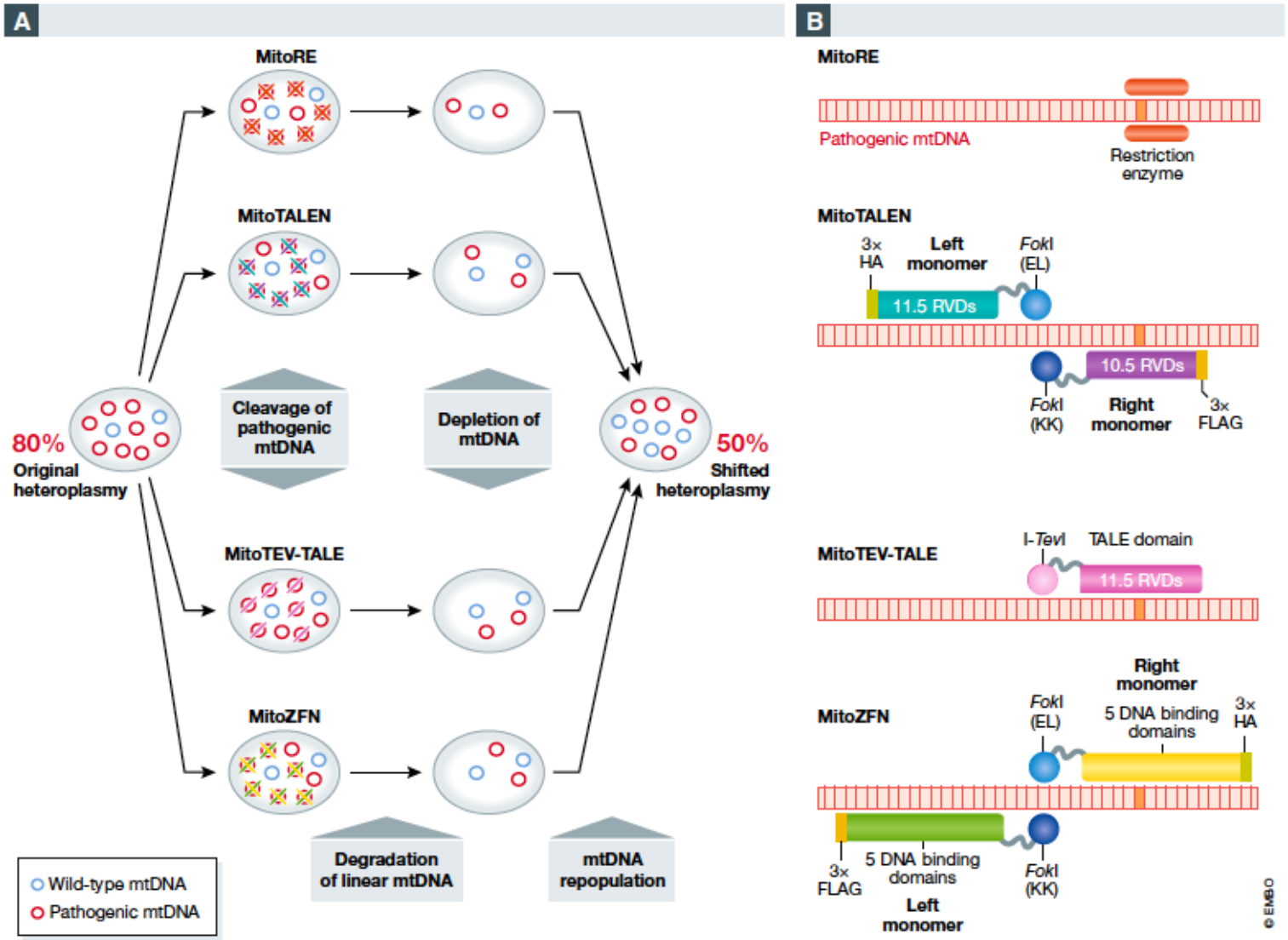
LHON GENE THERAPY GOES TRUE!

the validation (PPQ) batches required for marketing approval (GenSight Biologics Provides Update on LUMEVOQ® Manufacturing Timeline – GenSight Biologics (gensight-biologics.com). The Company is working with its manufacturing partner to implement targeted corrections around enhanced process control and more rigorous supervision inside the manufacturing suites. In addition, smaller engineering lots will be used to confirm the robustness of the corrective actions.

GenSight targets the restart of the PPQ campaign in Q3 2022. In the meantime, the Company has already finalized the responses to the D120 questions that were not related to the validation batches.

Responses to the Day 120 questions are now due in October 2022, after which regulatory review of LUMEVOQ®'s Marketing Authorisation Application will resume. The Company expects the opinion from the EMA's Committee for Medicinal Products for Human Use (CHMP) by Q3 2023, to be followed by commercial launch by the end of 2023.

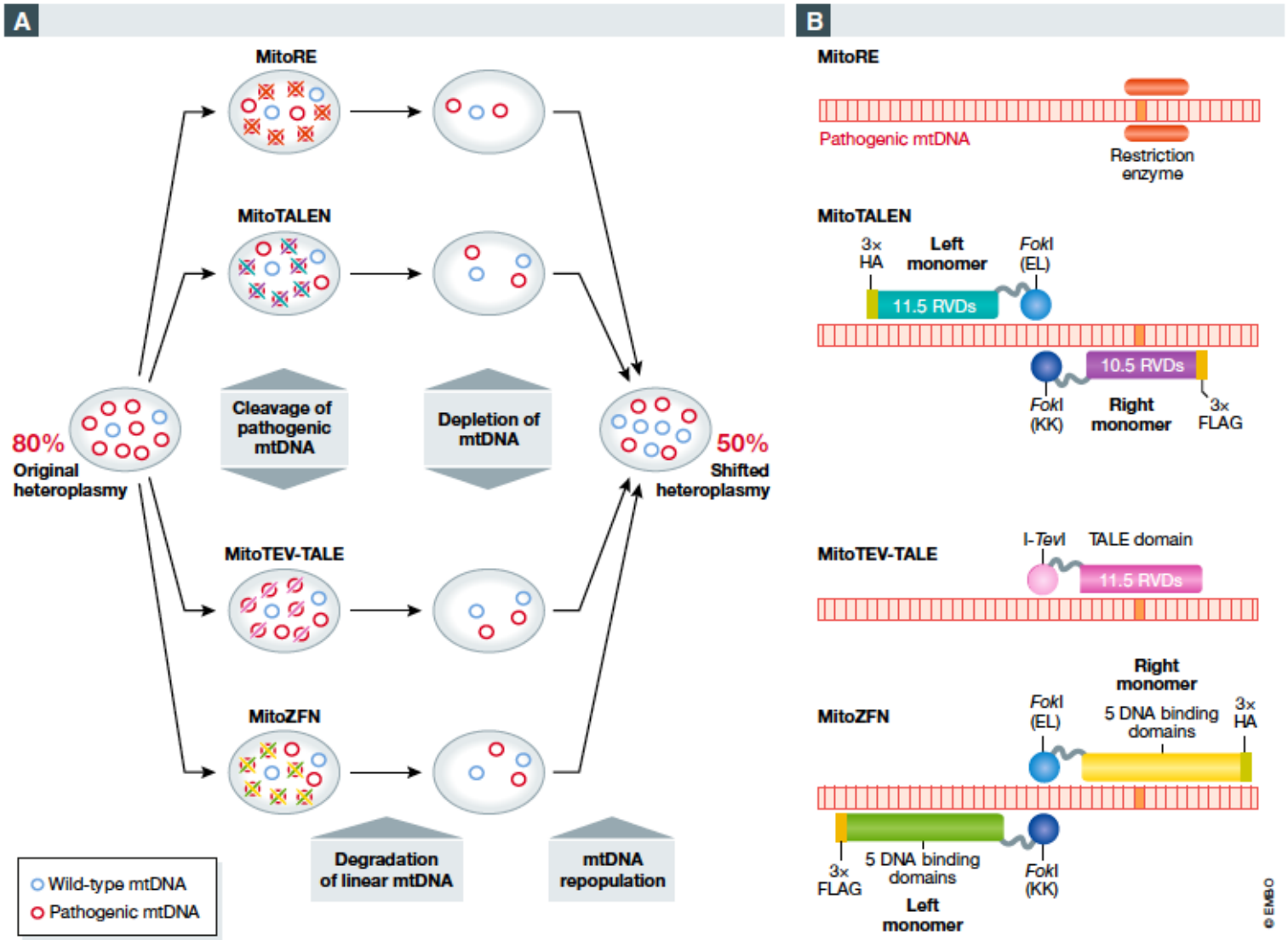
"*We are highly appreciative and grateful for the flexibility that the CAT has shown during the review of LUMEVOQ's regulatory filing,*" commented **Bernard Gilly**, Chief Executive Officer and Co-Founder of GenSight Biologics. *"The additional time granted allows us to implement the necessary adjustments with our manufacturing partner to ensure that LUMEVOQ is reliably and consistently produced at the scale needed for the upcoming commercial launch. These measures are part of our commitment to providing LHON patients with access to our innovative treatment as soon as possible."*



Nadee Nissanka & Carlos T Moraes, 2020

What is Mitochondrial Editing?

- Mitochondria do not allow any nucleic acid to enter their inner compartment
- No direct nucleic-acid based gene therapy is possible for mtDNA mutations
- For heteroplasmic mutations, molecular tools are available to eliminate mutant mtDNA species and promote wildtype mtDNA proliferation



Nadee Nissanka & Carlos T Moraes, 2020

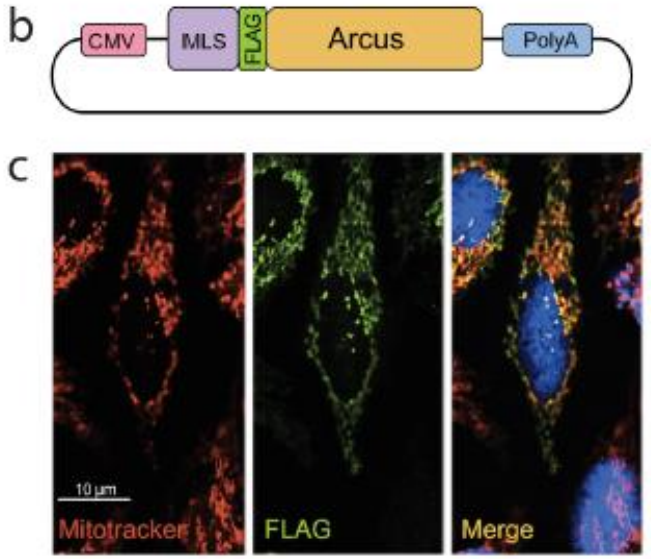
ARTICLE

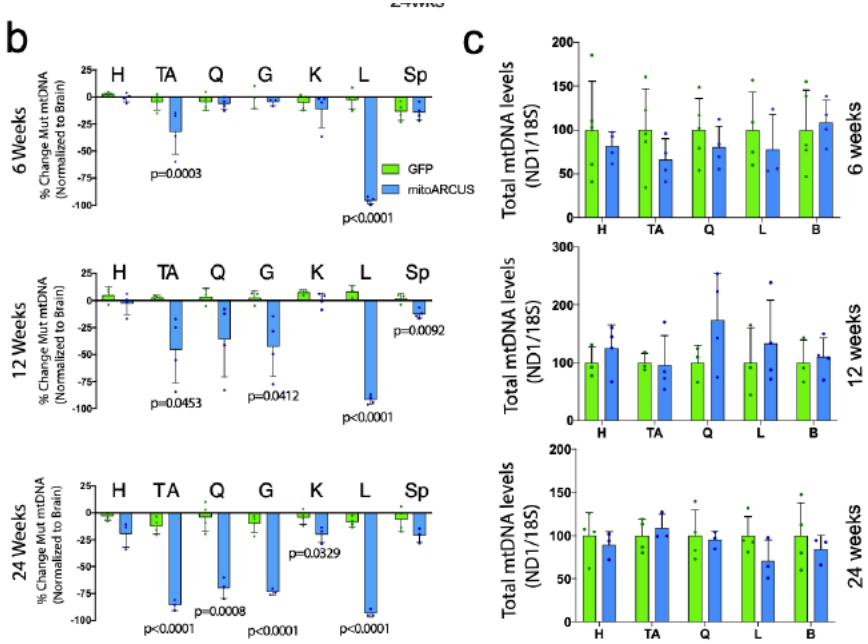
https://doi.org/10.1038/s41467-021-23561-7 OPEN

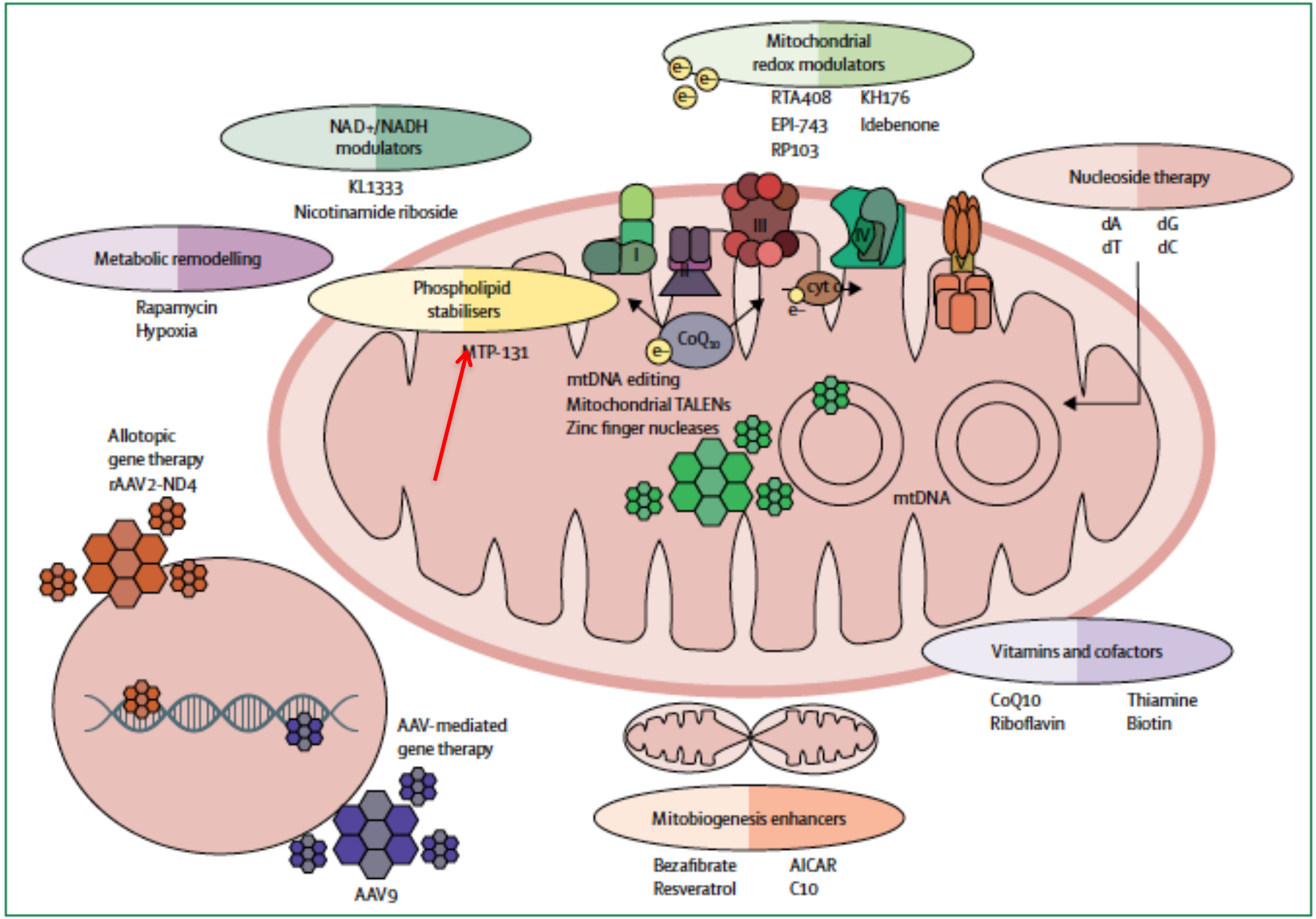
Check for updates

Mitochondrial targeted meganuclease as a platform to eliminate mutant mtDNA in vivo

Ugne Zekonyte[1], Sandra R. Bacman[2], Jeff Smith[3], Wendy Shoop[3], Claudia V. Pereira[2], Ginger Tomberlin[3], James Stewart[4,5], Derek Jantz[3] & Carlos T. Moraes[2]✉







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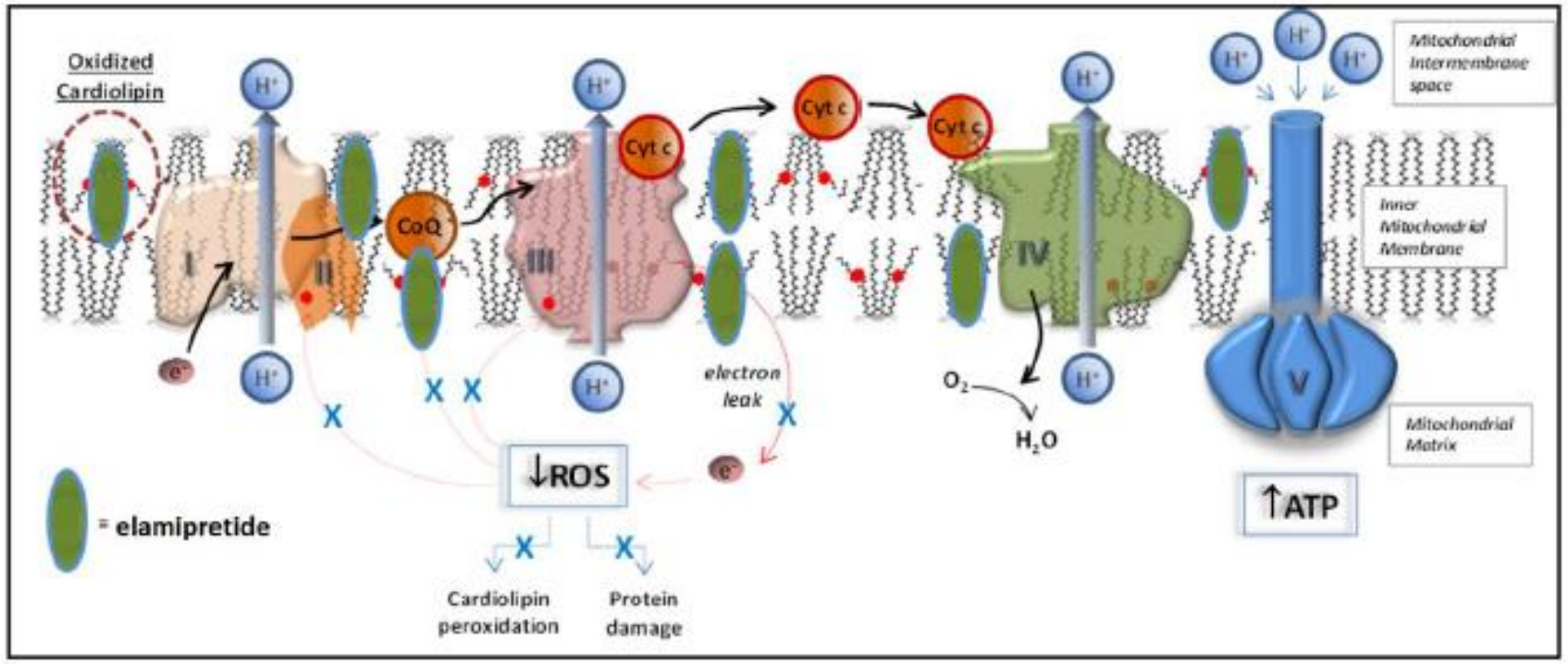
ELAMIPRETIDE

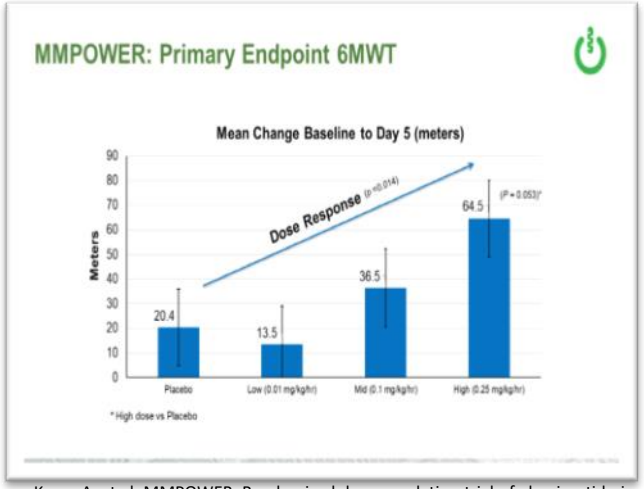
Small water-soluble mitochondrially-targeted tetrapeptide (D-Arg-dimethylTyr-Lys-Phe-NH2) that scavenges mitochondrial reactive oxygen species, inhibits the mitochondrial permeability transition pore and stabilizes cardiolipin.

Elamipretide has been shown to enhance ATP synthesis in multiple organs, including heart, kidney, neurons, and skeletal muscle.

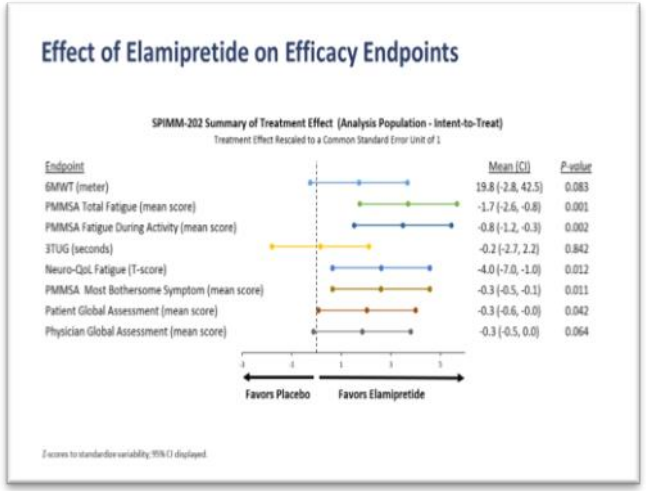


MMPOWER Program: clinical development of elamipretide for patients with primary mitochondrial myopathy (PMM)

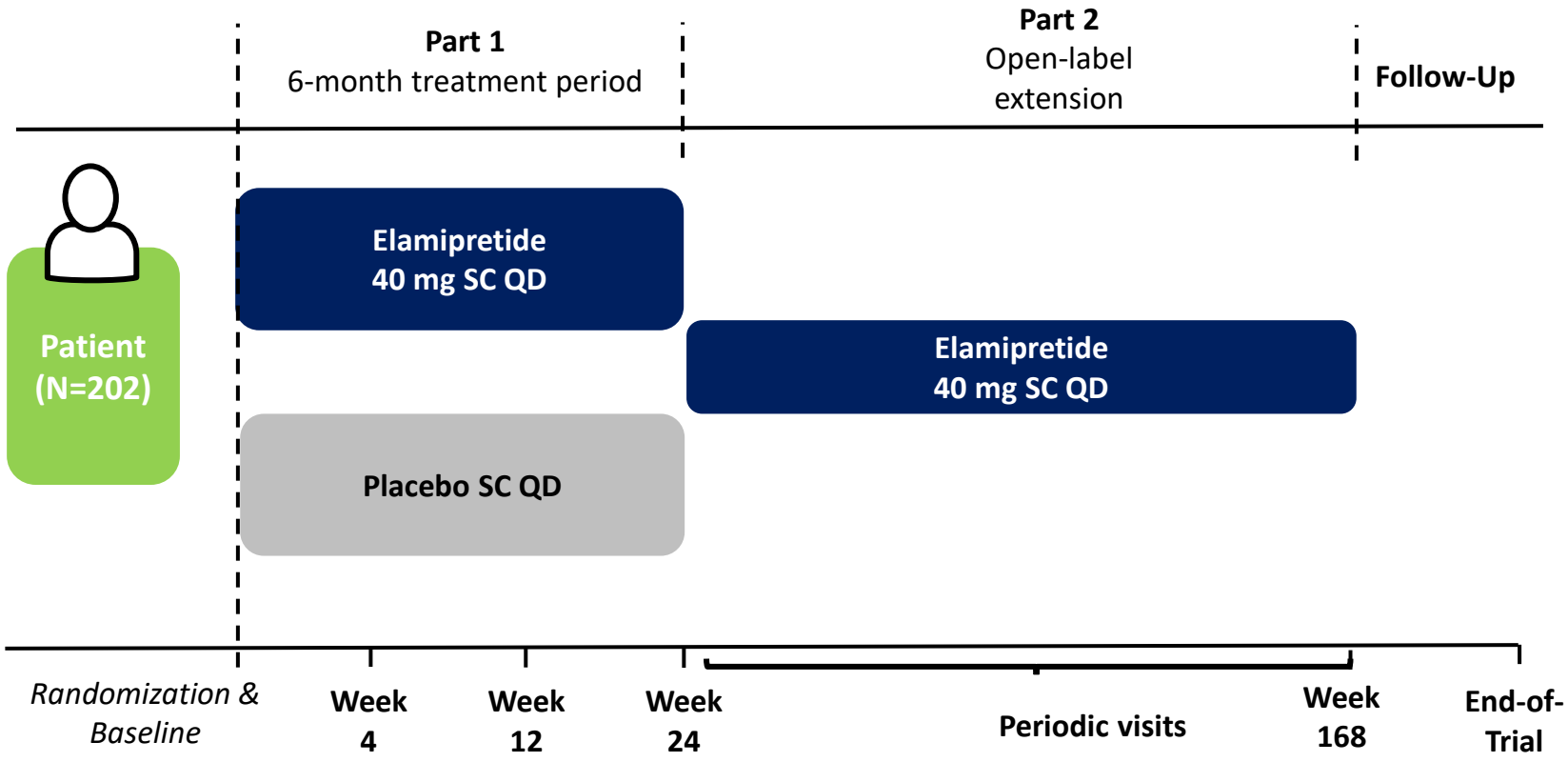
- MMPOWER Trial: Phase 1/2
- MMPOWER-2 Trial: Phase 2
- RePOWER Study
- MMPOWER-3 Trial: Phase 3



Karaa A, et al. MMPOWER: Randomized dose-escalation trial of elamipretide in adults with primary mitochondrial myopathy, *Neurology* Mar. 2018



Trial Design: MMPOWER-3



Phase 3 Study Design: Efficacy and Safety of Elamipretide in Subjects with Primary Mitochondrial Disease Resulting from Pathogenic Nuclear DNA Mutations (nPMD)

Amel Karaa[1] and Michelangelo Mancuso[2]

[1]Genetics Unit, Massachusetts General Hospital, Boston, MA 02114; [2]Azienda Ospedaliero Universitario Pisana, Pisa, Italy

INTRODUCTION AND RATIONALE

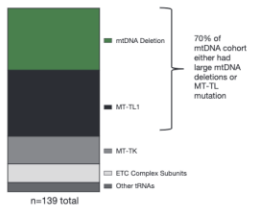
- Several clinical trials designed to identify novel treatments for primary mitochondrial myopathy are either complete or in progress
- The mitochondria-targeting peptide elamipretide was recently assessed in a Phase 3, randomized, double-blind, placebo-controlled clinical trial for the treatment of patients (n=218) with primary mitochondrial myopathy (MMPOWER-3)
- Enrolled patients had a variety of pathogenic variants in either nuclear (nDNA) or mitochondrial DNA (mtDNA) genes that caused their myopathy
- Overall, the MMPOWER-3 trial did not meet the primary endpoints in the highly heterogeneous study cohort
- A *post-hoc* genetic subgroup analysis was performed using the MMPOWER-3 per protocol population in persons who successfully completed the full trial duration to assess response on the six-minute walk test (6MWT) based on gene variants

RESULTS

- In the MMPOWER-3 trial, 70% of patients in the mtDNA cohort either had large mtDNA deletions or MT-TL mutation (**Figure 1**)

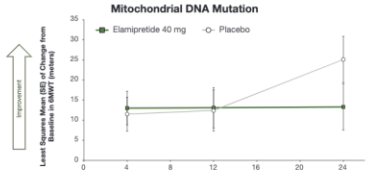
Figure 1. Genetic Breakdown of mtDNA Patients

- Majority of gene disruptions were:
  - mtDNA tRNAs (mostly leucine and lysine)
  - mtDNA deletions
  - mtDNA-encoded ETC subunits minority



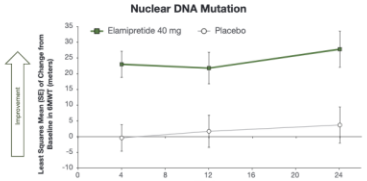
- Persons with mtDNA variants receiving elamipretide showed no significant effects on 6MWT when compared to placebo (**Figure 2**)
- After 24 weeks of elamipretide treatment, persons with nDNA gene mutations walked significantly farther than placebo counterparts ($p<0.05$) (**Figure 3**)

Figure 2. Change From Baseline in Distance Walked (meters) on 6MWT by Genetic Abnormality



Treatment Group	Week 4	Week 12	Week 24
Elamipretide (n=81)	80	78	74
Placebo (n=81)	78	76	75

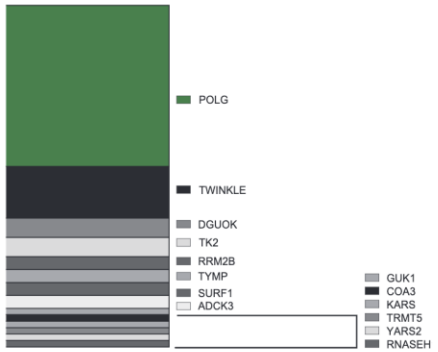
Figure 3. Change From Baseline in Distance Walked (meters) on 6MWT by Genetic Abnormality (continued)



Treatment Group	Week 4	Week 12	Week 24
Elamipretide (n=28)	28	28	26
Placebo (n=28)	27	26	27

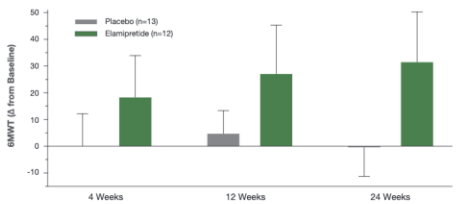
- Further analysis revealed this nDNA cohort was mostly comprised of persons with pathogenic variants required for mtDNA maintenance, including POLG (47%) and TWNK (15%) (**Figure 4**)
  - Generally, nDNA mutations account for ~23.2% of the clinically affected adults with mitochondrial disorders
  - For patients with nPMD from POLG1/2 mutations (comprise most of these patients), a database of all known case studies reports 681 total cases (n=369 for subjects ≥12-years-old)

Figure 4. Genetic Breakdown of nDNA Patients



- 6MWT at week 24 in *POLG* patients changed 32±19 versus -0.5 ±11 meters in placebo (n=12-13 per group) (**Figure 5**)

Figure 5. Change From Baseline in Distance Walked (meters) on 6MWT in Patients with Pathogenic POLG Variants



- No relationship was discernible among the loci of POLG variant(s) and elamipretide response, suggesting that 6MWT improvements were not limited to specific pathogenic cluster(s) along the POLG enzyme
- In addition, pharmacokinetic analyses in the nDNA cohort showed a positive correlation between plasma elamipretide concentration and 6MWT improvement

OBJECTIVE

In an effort to further elucidate the efficacy of elamipretide, a Phase 3, randomized, double-blind, placebo-controlled clinical trial (SPIMD-301) has been initiated to build upon the SPIMM-301 nDNA subgroup findings (specifically as it pertains to the replisome genes).

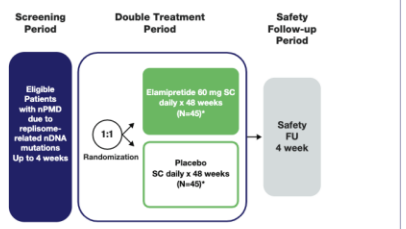
- This sub-group of patients with mutations in replisome genes seem to have responded differently to elamipretide and may have unique genotypic and biochemical characteristics to explain this preferential response.
- SPIMD-301 is designed to confirm the observed signals by enrolling and studying a similar group of patients with mitochondrial replisome mutations.

METHODS

- Subjects with primary mitochondrial disease (PMD), resulting from pathogenic nPMD mutations causing their myopathy, will receive a single daily subcutaneous dose of elamipretide 60 mg for 48 weeks (**Figure 6**)
- SPIMD-301 (NuPOWER) will enroll approximately 130 subjects (≥18 years and ≤ 70 years of age at the time of screening) consisting of 90 subjects who have nPMD associated with pathogenic mutations of the mitochondrial replisome ("replisome-related mutations") for primary analysis
  - Will include an additional subset of up to 40 subjects with nPMD associated with other non-replisome-related mutations

SPIMD-301 (NuPOWER) STUDY DESIGN

Figure 6. SPIMD-301 Study Design



* Up to 40 additional patients with non-replisome nDNA mutations will also be included/enrolled

- Inclusion criteria requires a diagnosis of nPMD with a predominant clinical manifestation of myopathy
  - Must include PEO and exercise intolerance and/or skeletal muscle weakness, with genetic confirmation of nDNA mutation of the mitochondrial replisome (replisome-related mutation)
  - The replisome includes the following genes: POLG 1/2, TWINKLE (C10ORF2), TYMP, DGUOK, TK2, RRM2B, RNASEH1, SSBP, MGME1, DNA2, ANT1 (SLC25A4), SUCLG1, SUCLA2, MPV17
- Primary efficacy endpoint: distance walked (meters) on the 6MWT
- Secondary endpoints: changes in the total time (seconds) for the Five-Times Sit-to-Stand Test (5XSST), total time (seconds) for the Triple Timed Up-and-Go Test (3TUG), and Patient Global Impression (PGI) of Change Scale
- Exploratory endpoints: EuroQol 5 Dimension 5 Level Questionnaire [EQ-5D-5L], Clinician Global Impression (CGI) of Change Scale, and most bothersome symptom on the Primary Mitochondrial Myopathy Symptom Assessment [PMMSA]
- Biomarkers and pharmacokinetic evaluations will also be explored
- Follow-Up Period will begin after completion of the Week 48 Visit and will last for 4 weeks

CONCLUSIONS

- Nuclear encoded control of mtDNA maintenance and replication may have particular relevance for elamipretide MOA in this patient population.
- Basket trial design introduced both genotypic and phenotypic heterogeneity that may have ultimately compromised the ability to see a treatment effect.
- Exposure-response relationship may differ by genotype/phenotype.
- There remains a high unmet need in this patient population, particularly with respect to weakness and fatigue during activities.
- Objective, reliable and validated endpoints to measure muscle weakness and fatigue are needed.

Disclosures

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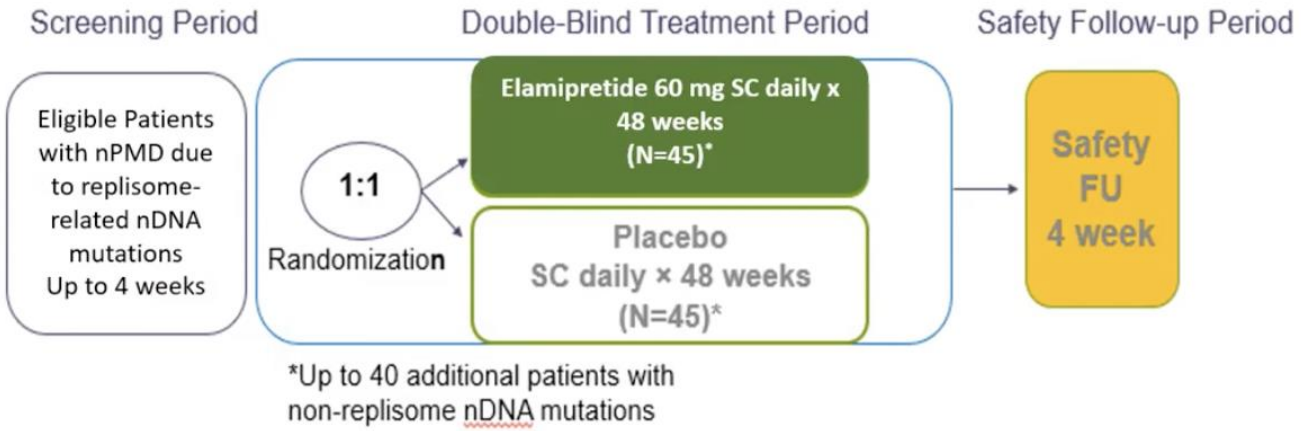
Medical writing assistance was provided by David A. Brown, Ph.D., Stealth BioTherapeutics, and James A. Shiffer, RPh, Write On Time Medical Communications, LLC

Stealth BIOTHERAPEUTICS

SPIMD-301 (NuPOWER) Phase 3 Trial Design

Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Daily Subcutaneous Injections of Elamipretide in Subjects with Primary Mitochondrial Disease Resulting from Pathogenic Nuclear DNA Mutations (nPMD)



- Primary clinical manifestation of myopathy, but enriching for replisome-related nDNA mutations + PEO co-morbidity
- 6MWT primary endpoint; 5XSST, 3TUG, PROs as secondary endpoints
- 1-year treatment duration
- Initiation Q4 2021

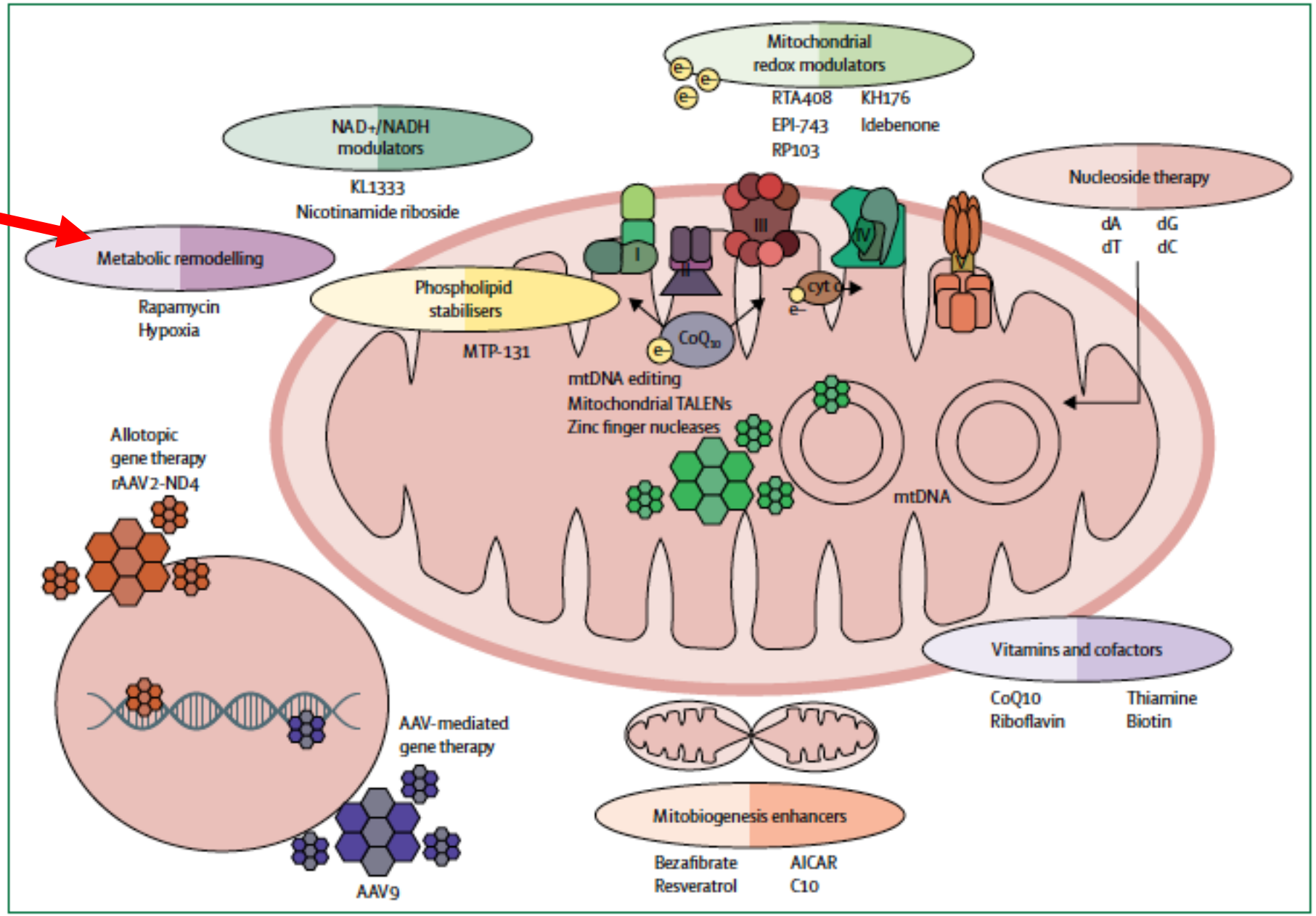


Figure 3: **Mitochondrial therapies in development**

Despite the absence of approved curative therapies for mitochondrial disease, several pharmacological and genetic approaches to ameliorating the pathology of mitochondrial disease are under investigation. mtDNA=mitochondrial DNA.

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Hypoxia as a Therapy for Mitochondrial Disease

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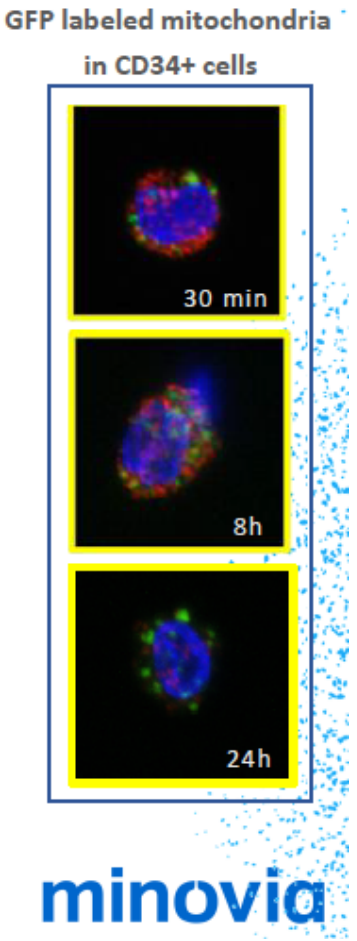
Abstract

Defects in the mitochondrial respiratory chain (RC) underlie a spectrum of human conditions, ranging from devastating inborn errors of metabolism to aging. We performed a genome-wide, Cas9-mediated screen to identify factors that are protective during RC inhibition. Our results highlight the hypoxia response, an endogenous program evolved to adapt to limiting oxygen availability. Genetic or small molecule activation of the hypoxia response is protective against mitochondrial toxicity in cultured cells and zebrafish models. Chronic hypoxia leads to a marked improvement in survival, body weight, body temperature, behavior, neuropathology and disease biomarkers in a genetic mouse model of Leigh syndrome, the most common pediatric manifestation of mitochondrial disease. Further preclinical studies are required to assess whether hypoxic exposure can be developed into a safe and effective treatment for human diseases associated with mitochondrial dysfunction.

MITOCHONDRIAL CELL THERAPY

- It was shown before that isolated mitochondria can re-enter cells (Clark Nature 1982) and that cells can transfer mitochondria to neighboring cells (Spees PNAS 2006)
- Minovia is the first company to use a cell therapy approach to treat mitochondrial diseases, through our Mitochondrial Augmentation Therapy (MAT) platform
- MAT introduces healthy mitochondria to the patient by using autologous stem cells enriched with normal mitochondria from a healthy donor, targeting the etiology of primary mitochondrial diseases
- Minovia's end products are high-quality mitochondrial augmented cells
- Mitochondria, the critical intermediate product, are manufactured by our proprietary process from either an allogeneic or syngeneic source



Mitochondrial Augmentation Therapy (MAT)

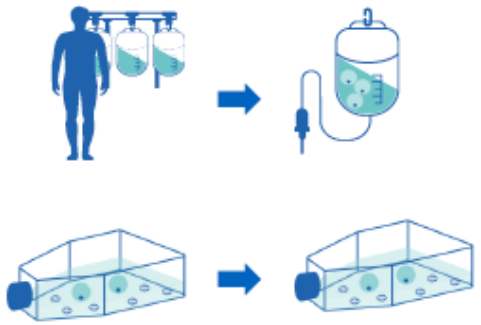
No conditioning of patients, no immunosuppression, short manufacturing time

Mitochondria

Qualified proprietary products from a healthy donor (allogeneic or syngeneic)

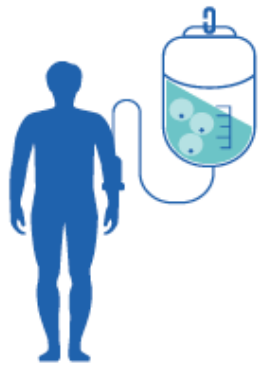
Augmentation

Harvest autologous CD34+ cells from peripheral blood of the patient and produce our proprietary mitochondrial augmented cell product



Therapy

Adoptive Mitochondrial Transfer step: Infuse patient with mitochondrially augmented CD34+ cells



40h Vein – To – Vein Process

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