Mitochondrial Therapeutics for Optic Nerve Dysfunction

Conflict of Interest Disclosure

- I have no potential conflict of interest to disclose

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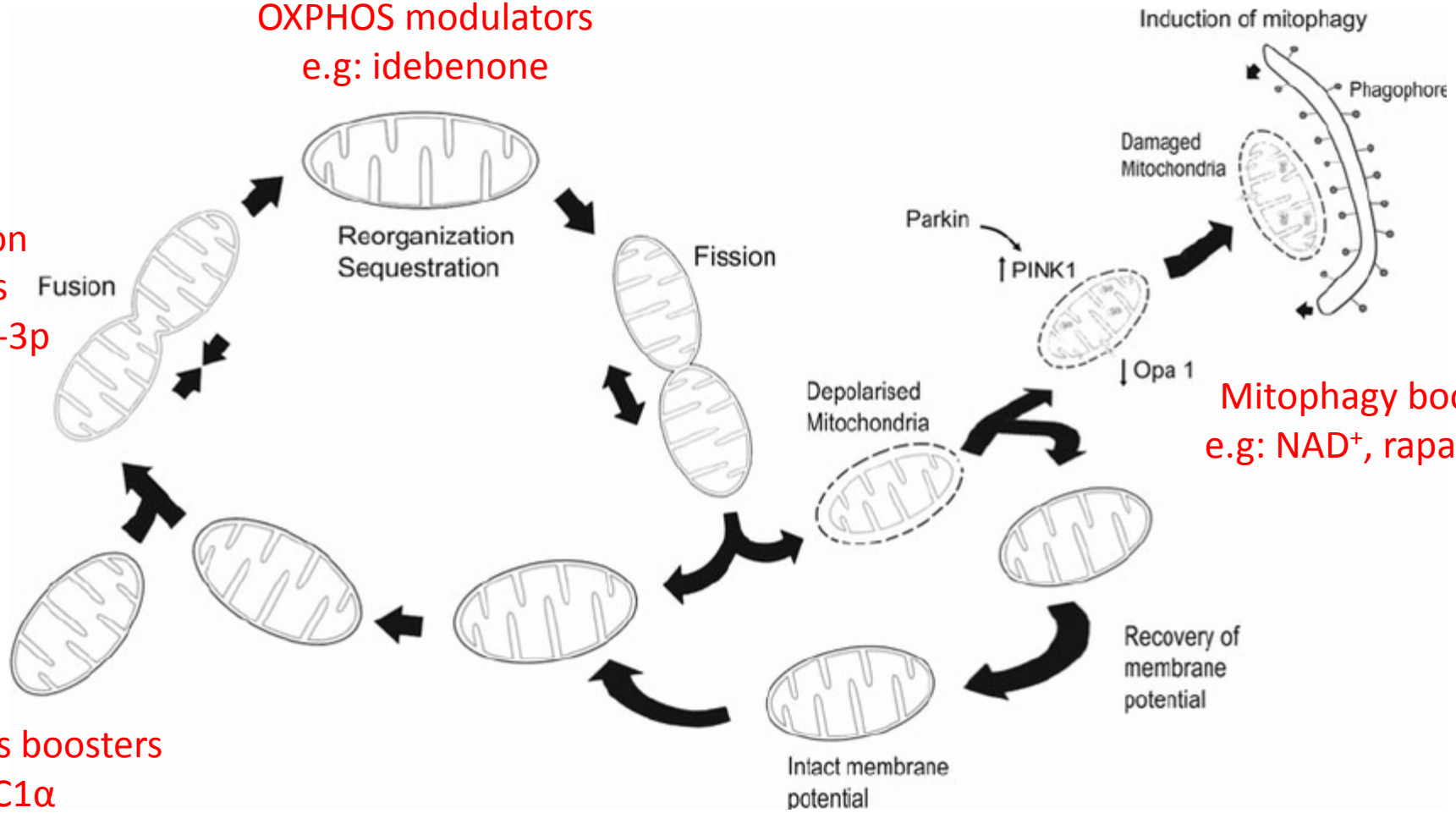
Outline

- Mitochondrial life cycle
- Evidence for mitochondrial dysfunction in optic nerve disease
  - Optic neuropathies: Genetic evidence
  - POAG: Biochemical and genetic evidence
- Therapeutic approaches

Mitochondrial life cycle

OXPHOS modulators
e.g: idebenone

Fission/fusion
modulators
eg: miR-376b-3p



Mitophagy boosters
e.g: NAD^+, rapamycin

Biogenesis boosters
PGC1α
e.g: fibrates, AMPK activators

(Modified from: Lim et al Antiox Redox Signalling 2011)

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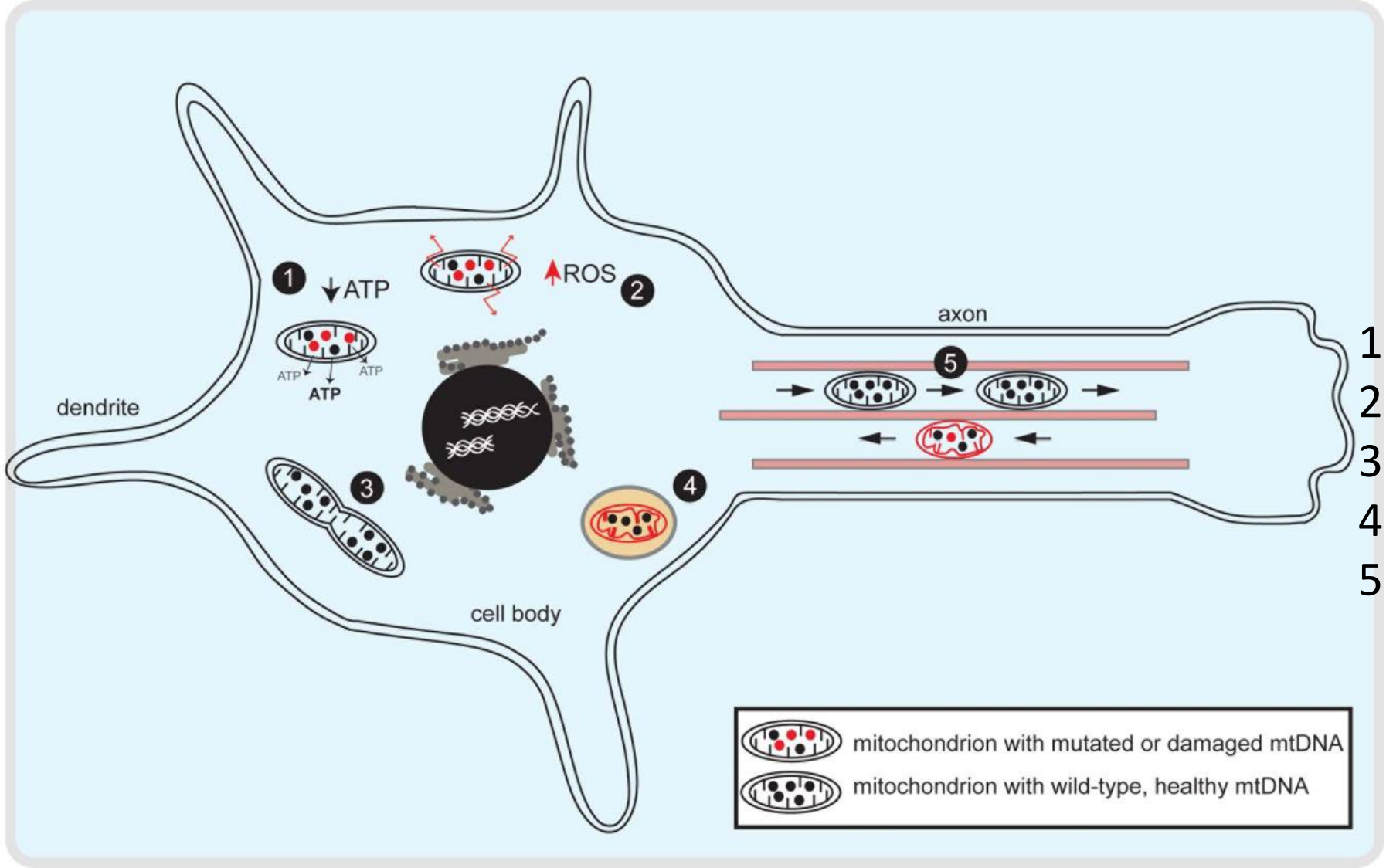
Potential mitochondrial mechanisms of retinal ganglion cell dysfunction



1. Bioenergetic decline
2. Increased ROS
3. Defective fission/fusion
4. Impaired mitophagy
5. Impaired axonal transport

Lopez Sanchez et al Pharm Therap 2016

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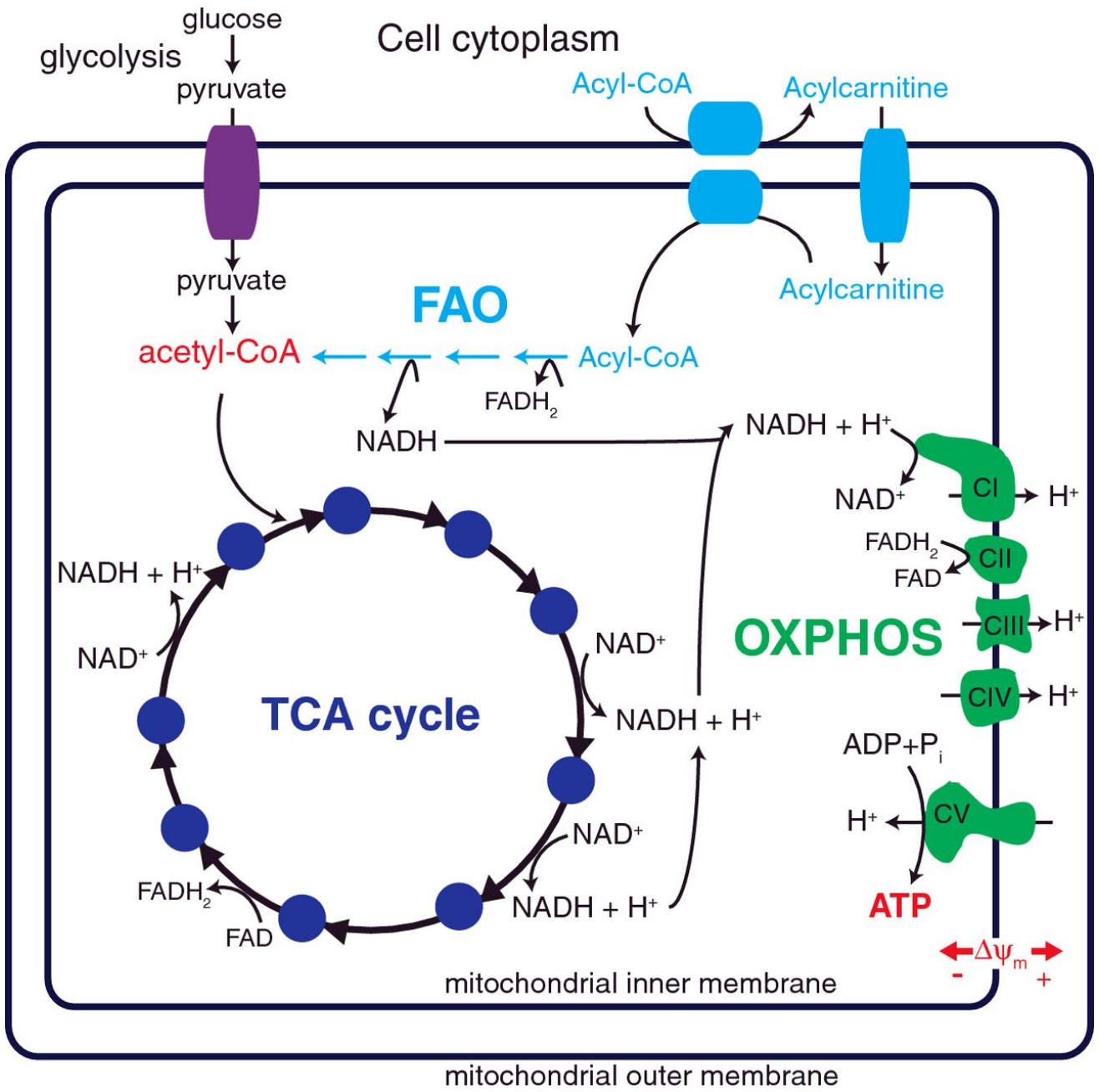
Optic neuropathy in mitochondrial disease – genetic clues

Disease	Gene/protein	Function	Phenotype
LHON	mtDNA	OXPHOS CxI	Optic atrophy
ADOA ADOA *plus* LHON *plus*	OPA1 OPA1 mtDNA	Mitochondrial fusion OXPHOS CxI	Optic atrophy Optic atrophy + ataxia, dystonia etc
Hereditary spastic paraplegia	Paraplegin (SPG7)	Mitochondrial metallo-protease	Dystonia plus optic atrophy
Charcoat-Marie-Tooth 2A	Mitofusin2	Mitochondrial fusion	Neuropathy plus optic atrophy



OXPHOS:
Oxidation of NADH
replenishes NAD+
for TCA cycle

Many cells can do without OXPHOS
For ATP production, but
cannot do without TCA cycle
for providing precursors for
nucleotide, amino acid and lipid
synthesis

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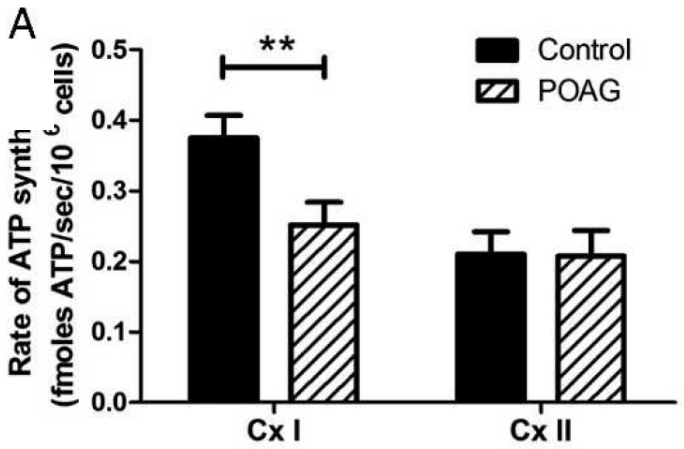
Nsiah-Sefaa & McKenzie Bioscience Reports 2016

POAG study I – Melbourne cohort

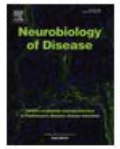


Lee et al IOVS 2012

ELSEVIER

Neurobiology of Disease

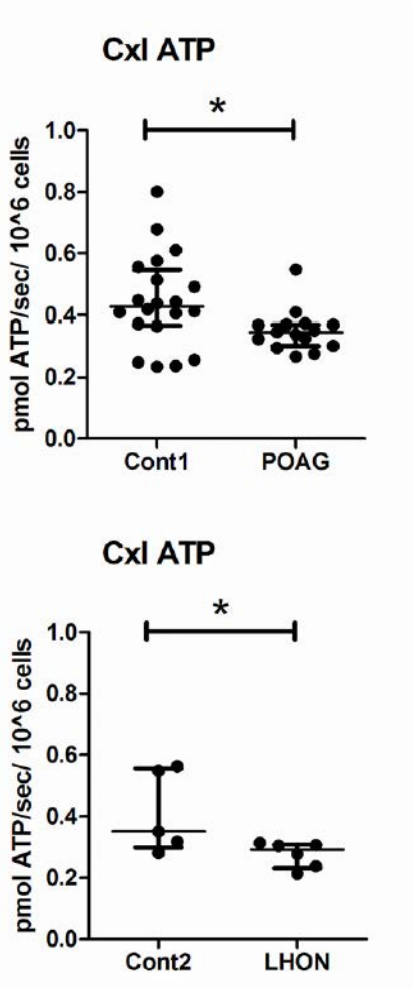
Volume 82, October 2015, Pages 78-85



Resistance to the most common optic neuropathy is associated with systemic mitochondrial efficiency

Gerassimos Lascaratos [a], Kai-Yin Chau [b], Haogang Zhu [c], Despoina Gkotsi [a], Rosalind King [b], Ivan Gout [d], Deborah Kamal [a], Philip J. Luthert [a, e], Anthony H.V. Schapira [b], David F. Garway-Heath [a]

POAG study II – Adelaide cohort and LHON comparison



POAG

LHON

Van Bergen et al PlosOne 2015

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mtDNA studies in POAG

Glaucoma

Mitochondrial DNA Variation and Disease Susceptibility in Primary Open-Angle Glaucoma

Larry N. Singh,[1] Jonathan G. Crowston,[2] M. Isabel G. Lopez Sanchez,[2] Nicole J. Van Bergen,[2] Lisa S. Kearns,[2] Alex W. Hewitt,[2,3] Seyhan Yazar,[4,5] David A. Mackey,[4] Douglas C. Wallace,[1,6] and Ian A. Trounce[2]

(IOVS 2018)

Small study (95 POAGs, 95 population controls)
- showed protective effect of haplogroup U in males

Wolf *et al. BMC Genetics* 2010, **11**:8
http://www.biomedcentral.com/1471-2156/11/8

BMC Genetics

RESEARCH ARTICLE Open Access

Mitochondrial haplogroup U is associated with a reduced risk to develop exfoliation glaucoma in the German population

Christiane Wolf[1†], Eugen Gramer[2†], Bertram Müller-Myhsok[3], Francesca Pasutto[4], Bernd Wissinger[1], Nicole Weisschuh[1*]

ELSEVIER

Experimental Eye Research
Volume 181, April 2019, Pages 85-89

Small study (272 NTG POAGs, 157 PXF POAGs)
- showed protective effect of haplogroup U in PXF, trend in NTG

The association of mitochondrial DNA haplogroups with POAG in African Americans

Harini V. Gudiseva [a], Maxwell Pistilli [a], Rebecca Salowe [a], Larry N. Singh [b], David W. Collins [a], Brian Cole [c], Jie He [a], Sayaka Merriam [a], Naira Khachataryan [a], Jeffrey Henderer [d], Victoria Addis [a], Qi N. Cui [a], Prithvi S. Sankar [a], Eydie Miller-Ellis [a], Venkata R.M. Chavali [a], Gui-Shuang Ying [a], Douglas Wallace [b], Joan M. O'Brien [a]

Large study (2000 POAGs, 2000 controls)
- showed risk effect of non-L haplogroups in males

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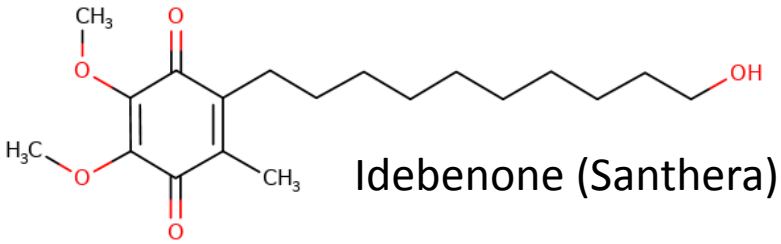
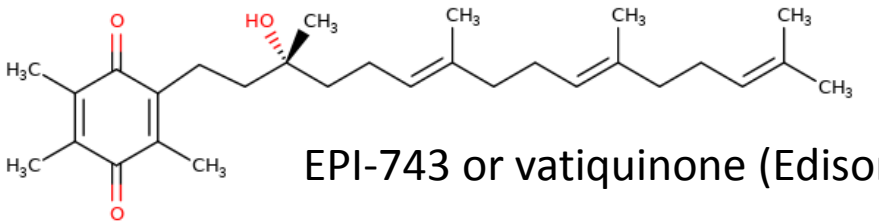
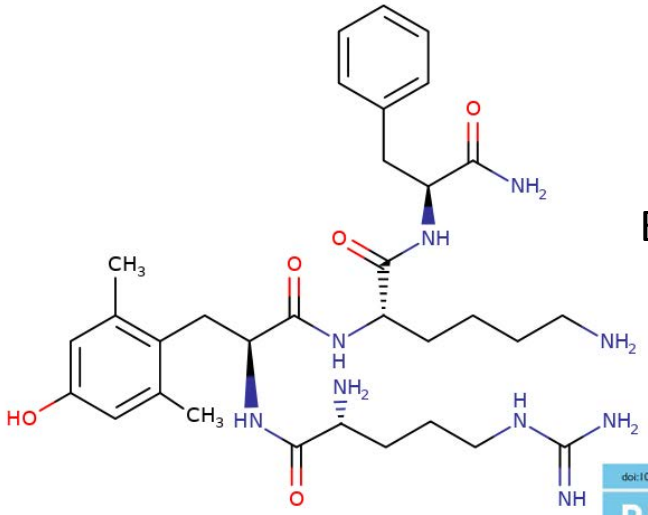
Mitochondrial therapeutics – In practice



Idebenone (Santhera)



EPI-743 or vatiquinone (Edison)



Elamipretide or SS-31 (Stealth)

NAD+ precursors

RESEARCH

REPORT

GLAUCOMA

Vitamin B_3 modulates mitochondrial vulnerability and prevents glaucoma in aged mice

Pete A. Williams,[1] Jeffrey M. Harder,[1] Nicole E. Foxworth,[1] Kelly E. Cochran,[1] Vivek M. Philip,[1] Vittorio Porciatti,[2] Oliver Smithies,[3] Simon W. M. John[1,4,5*]

Insulin, IGF-1

doi:10.1093/brain/awy142 BRAIN 2018: 141; 1963–1980 | 1963

BRAIN
A JOURNAL OF NEUROLOGY

Insulin signalling promotes dendrite and synapse regeneration and restores circuit function after axonal injury

Jessica Agostinone,[1,2] Luis Alarcon-Martinez,[1,2] Clare Gamlin,[3] Wan-Qing Yu,[3] Rachel O. L. Wong[3] and Adriana Di Polo[1,2]

SCIENTIFIC REPORTS

Article | OPEN | Published: 27 October 2017

Norrin protects optic nerve axons from degeneration in a mouse model of glaucoma

Stephanie A. Leopold, Ludwig F. Zeilbeck, Gregor Weber, Roswitha Seitz, Michael R. Bösl, Herbert Jägle, Rudolf Fuchshofer, Ernst R. Tamm & Andreas Ohlmann

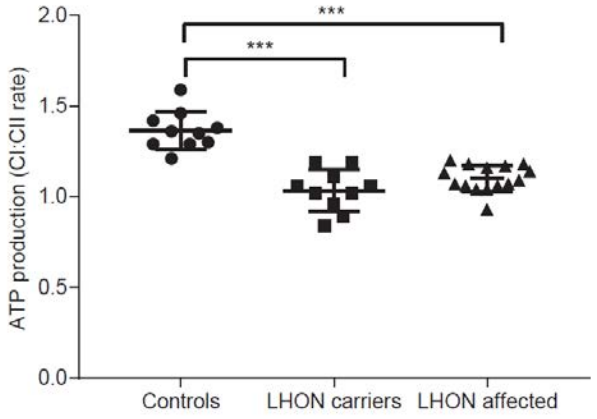
Scientific Reports **7**, Article number: 14274 (2017) | Download Citation

LHON: No evidence of OXPHOS compensation protecting carriers

The nucleus fights back: RNA-seq analysis of LHON affected and LHON carrier fibroblasts

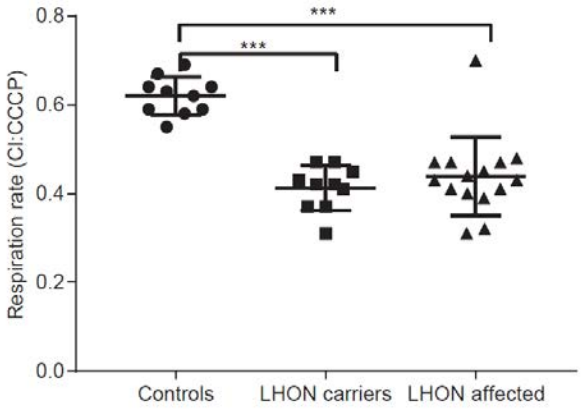
A

Maximal CxI-linked ATP production



B

Maximal CxI-linked respiration rate



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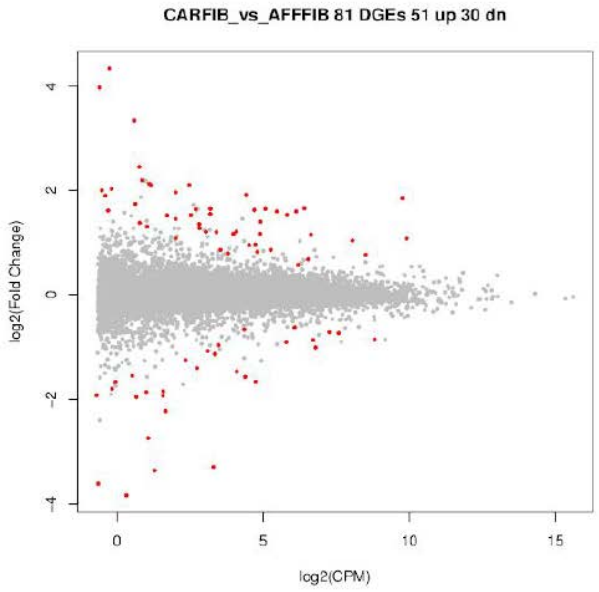

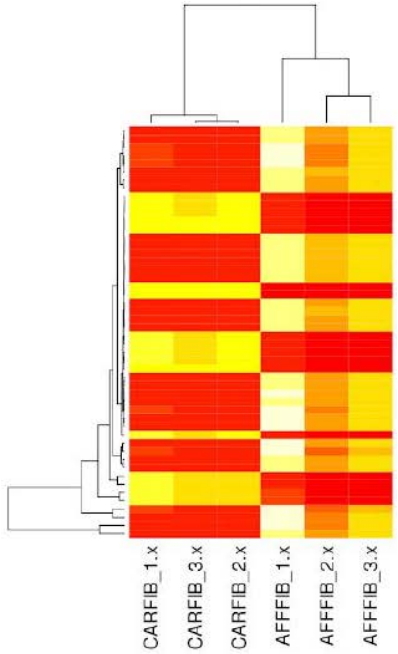

MA plots and heatmaps

All donors male, mtDNA haplogroup H, all m.11778G>A (ND4)

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What I want to know

- Do mild OXPHOS defects (as in LHON) impact on organelle turnover/quality control - is the bioenergetic defect key or a distraction

- Can mtDNA variants combine with nuclear mitochondrial gene variants to increase risk of sporadic neurodegenerative disease – POAG, Parkinson's

What we lack

- Uniform cellular and mouse models of OXPHOS-linked RGC-specific loss for pathogenic insights and molecular screening

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