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Towards a treatment for mitochondrial disease: current compounds in clinical development

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Reviewer 1

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*Only major points from review and responses included.

Reviewer 1

Section 2.1
"NADH:quinone oxidoredutase (NQO1) is an antioxidant cytoplasmic flavoprotein that reduces quinones into hydroquinones by transferring two electrons from NADH to NAD^+" Electrons are not transferred from NADH to NAD^+ but rather NADH is converted to NAD^+ and the electrons are transferred to the quinones. Thus the sentence needs to be rewritten to communicate clearly what is taking place.

Authors

We have corrected this sentence.

Reviewer 1

"Mitochondrial biogenesis can increase the cell efficiency by requiring less oxygen to produce an equal amount of energy and by reducing ROS production [19]." It is totally unclear why and how the generation of more mitochondria results in reduced ROS production. Is this a mere correlation reported by the authors in the cited publication or is it a speculation? Asserting this as a fact is problematic as it has no mechanistic basis. Either the authors briefly explain this or delete the assertion.

Authors

We have removed this sentence.

Reviewer 1

"In vitro studies in MELAS patient cells showed that KL1333 was able to restore NAD+/NADH levels through NQO1 activity" From the presentation it seems that KL1333, being a quinone, would act as a recipient of electrons from NADH increasing NAD+ concentrations. Of course it could not simply act as a substrate but would need to pass electrons on and that seems to be cytochrome. The cell-free experiment is essential to viable proposed mechanism but the way it is presented is confusing.

Authors

We have added a more detailed explanation of NQO1 and quinones to make the text more comprehensive.

Reviewer 1

Section 2.2

" Complex I (CI) dysfunction, one of the most common mitochondrial impairments, can cause a NAD+/NADH imbalance and a decrease in mitochondrial membrane potential" The use of the word "imbalance" makes the process unclear. There is no balance. Either the ratio is increased or decreased. Since complex 1 oxidizes NADH, the ratio probably decreases.

Authors

This sentence has been corrected.

Reviewer 1

"NV189, the first generation of permeable succinate prodrugs, was able to ameliorate the increase of lactate production in chemically CI-inhibited human platelets and increase the spare respiratory capacity of Leigh syndrome patient-derived fibroblasts [34]." The use of a compound that is converted to succinate after entering cells would be expected to have limited use except in in vitro experiments with isolated cells. In that situation there would be enough substrate in the medium to have a positive effect on the cells. However, as a substrate, large amounts would be needed to affect the energetics of a person. This seems very unfeasible unless something else is taking place. Without pointing out this problem, the presentation is misleading.

Authors

The question about how much succinate needs to be delivered to ameliorate the insufficient energy metabolism in mitochondrial disease is certainly a very important one. Direct substrate supply to the ETS as well as anaplerosis of the Kreb's cycle and re-establishment of normal succinate levels may all play a role. To the latter point, lower levels of succinate have been reported in the Ndufs4 model (Terburgh et al. 2019, 2021) suggesting an increased use of succinate accompanied by a lack of resupply of substrates from a congested Kreb's cycle. Inhibition of complex I in cells also seem to deplete succinate (Shaham et al 2010). These references have been included in the manuscript. Experimental proof of concept studies in cells with the first generation of succinate prodrugs are summarized in the manuscript. In vivo studies with NV354 in Ndufs4 knock-out mice and other models have been performed, but these are not cited as the studies are being prepared for publishing right now.

Reviewer 1

"MT1621 is about to be evaluated in a Phase III single-arm study in children and adolescents, primarily evaluating the proportion of subjects acquiring a motor milestone." This could be stated differently so as to clearly relate the possible outcome as opposed to using the term "motor milestone".

Authors

The term 'motor milestone' is frequently used in regard to pediatric motor system development and is also the term used for the endpoints in this specific trial. The sentence has been completed with some additional information that is available publicly.

Reviewer 1

Section 2.3

"Pathological ROS levels due to dysfunction in the oxidative phosphorylation system (OXPHOS) can lead to oxidative stress, imbalanced ROS production" What is a "balanced" ROS production much less an "imbalanced" ROS production?

Authors

Oxidative stress is defined as the imbalance between ROS production and cellular antioxidant capacity. We have now rephrased this sentence to make it more comprehensive.

Reviewer 1

" Barth syndrome is a primary mitochondrial disorder giving rise to symptoms such as skeletal muscle weakness and cardiomyopathy. Interestingly, Barth syndrome patients can present cardiolipin abnormalities" Some information on the nature of these abnormalities is quite necessary. Is cardiolopin is converted to a different molecule or is the change such that it is still cardiolipin but the properties are altered…e.g change in degree of unsaturation?

Authors

More information about the changes in cardiolipin in Barth syndrome has been added.

Reviewer 1

"The evaluation of long term exposure in an open label extension (part 2) resulted in an overall good tolerability of elamipretide with potential improvements over time [43]. " Did the trials show any significant improvement or is there just hope for the future? The latter possibility is not informative. A clarification is necessary.

Authors

This study was divided in two parts: part 1 with a placebo control and part 2: open label extension with comparisons from baseline. No changes were observed in part 1 for their primary endpoints but significant improvements in fatigue and 6MWT from baseline were observed in part 2. A more detailed explanation of the results and primary endpoints at each part have been added.

Reviewer 1

"When compared to Q10 and idebenone, vatiquinone presented up to ten-thousand times higher protective activity against oxidative stress [44, 45]" It is unclear how one could design an experiment that could detect such an enormous increase in protective activity. If true them more information needs to be presented so that the reader can appreciate the validity of that claim.

Authors

More information about the nature of the experiments has been added and the specific citation of the fold difference has been removed.

Reviewer 1

"Vatiquinone is currently being evaluated in a phase II/III with mitochondrial disease patients presenting refractory epilepsy to evaluate efficacy in observable motor seizures for 28 days as primary outcome." How does one "evaluate efficacy" of a seizure? Is it the duration of a seizure or the damage resulting from the seizure? I suspect the authors mean to say the efficacy in inhibiting seizures.

Authors

The sentence has been corrected.