Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

SKQ1

Evidence Summary

Preclinical studies suggest that SkQ1 might act as a geroprotector; unfortunately, most of the studies have been conducted at a single university.

Neuroprotective Benefit: Preclinical studies from a mouse model of accelerated aging suggest a potential benefit, but experiments have not been repeated by other laboratories.

Aging and related health concerns: Although SkQ1 extended lifespan in a number of species, effects are not consistent and little work has been conducted in humans.

Safety: No evidence for adverse effects in animal studies, although it has not been tested systemically in humans (other than in eye drops).

What is it?

The free radical theory of aging suggests that the accumulation of cellular damage by reactive oxygen species (ROS) is a major driver of the aging process. The failure of antioxidants to prevent or slow age-related diseases in numerous clinical trials has largely debunked this theory. However, some scientists suggest that specifically mitochondrial ROS drive the aging process, and antioxidants targeted to mitochondrial might be more beneficial. Support for the "mitochondrial free radical theory of aging" comes from experiments showing that over-expression of mitochondrial targeted catalase (an enzyme that can protect from ROS) extends lifespan in mice whereas over-expression of peroxisome or nuclear localized catalase fails to do so (Dai et al, 2014). Therefore, new antioxidants are being developed that specifically target mitochondria.

SkQ1 is a plastoquinone (an antioxidant) conjugated to a triphenyl-phosphonium cation (TPP+). In mitochondria, H+ ions are pumped out of the mitochondrial matrix into the intermembrane space. This causes a large negative potential gradient (about -150mV) across the inner mitochondrial membrane. The positive charge of the TPP+ portion of SkQ1 causes it to accumulate in the mitochondrial matrix, where much of the damage from ROS occurs. SkQ1 could be taken at low doses and hopefully will have a greater impact than other antioxidants (Dai et al, 2014).

Neuroprotective Benefit*:* Preclinical studies from a mouse model of accelerated aging suggest a potential benefit, but experiments have not been repeated by other laboratories.

Types of Evidence:

- Multiple preclinical studies in one rat model of accelerated aging

Human Evidence:

None

Rationale and evidence from animal studies:

SkQ1 was developed by Vladimir Skulachev at Moscow State University (see Josh Mittledorf blog). Unfortunately, there has not been widespread adoption of SkQ1, and most of the studies have been conducted at one university.

In a rat model of accelerated aging (OXYS rats), low doses of SkQ1 (250 nmol/kg) for 2-6 months was reported to prevent synaptic and neuronal loss, increase levels of synaptic proteins, enhance

neurotrophic supply (by an increased expression of BDNF receptors), decrease amyloid beta and phosphorylated tau in the hippocampus, decrease levels of mitochondrial DNA deletions, and improve some cognitive abilities. SkQ1 also reduced anxiety in OXYS rats and aged control rats but *reduced* spatial memory in control animals. The authors speculated that this reduction in spatial memory was due to a decrease in anxiety rather than a cognitive defect, per se (Stefanova et al, 2010; Stefanova et al, 2014; Stefanova et al, 2016, Isaev et al, 2016).

In a rat hippocampal slice culture model, a single administration of SkQ1 (or the related molecules SkQT1 and SkQR1) prevented amyloid beta-induced reduction in LTP (Kapay et al, 2013; Isaev et al, 2013; Genrikhs et al, 2015; Stelmashook et al, 2015). The OXYS rat model was developed by inbreeding Wistar rats with increased susceptibility to galactose-induced cataract formation. They have shortened lifespans and show signs of accelerated senescence, including cataract formation, senile osteoporosis, high blood pressure, and amyloid beta and phosphorylated tau aggregation (Obukhova et al, 2010, Stefanova et al, 2016). However, there is little work on OXYS rats, and no studies examined SkQ1 in more traditional animal models of Alzheimer's disease making comparison with other drugs difficult.

ApoE 4 interactions:
None reported

Aging and related health concerns: Although SkQ1 extended lifespan in a number of species, little work has been conducted in humans.

Types of evidence:

- Topical treatment - One human clinical trial for treatment of dry eyes
- Multiple animal lifespan studies (oral or IP)
- Multiple preclinical animal studies

Human studies:
In a phase 2 studies of patients with dry eyes (avg. age 62), SkQ1 in eye drops significantly improved dry eye symptoms over placebo.

Biology:
Lifelong treatment with SkQ1 extends lifespan in many species including fungi, crustaceans, drosophila, fish, and sometimes in mice (Anisimov et al, 2011, Rogovin et al, 2014). The effect may depend on the

immune system. In an extensive lifespan analysis, SkQ1's effects ranged from no effect to lifespan extension depending on the condition and rodent strain. Lifespan extension was more likely to occur in animals kept in non-sterile conditions where animals often die of infections (Anisimov et al 2011).

In addition to the lifespan studies, rodents treated with SkQ1 showed improved biomarkers of aging (measured by increased levels of growth hormone and IGF-1 in aged animals), decreased levels of aortic inflammation (measured with ICAM1 mRNA), faster wound healing, delayed cataract formation, and decreased senescence-associated cardiomyopathy, cardiac hypertrophy, and diffuse myocardial fibrosis (Kolosova et al, 2012; Zinovkin et al, 2014; Demyanenko et al, 2015; Manskikh et al, 2015, Stefanova et al, 2010).

Safety: No evidence for adverse effects in animal studies, although it has not been tested systemically in humans (other than in eye drops).

Types of evidence:

- Several preclinical studies

Animal studies and human clinical trials with eye drops have not reported adverse events with SkQ1. However, SkQ1 has yet to be given systemically in humans, and previous papers did not report a *lack of adverse effects*. SkQ1 accumulates in mitochondria which may raise concerns over long-term use even at low doses.

How to use?

Since SkQ1 is accumulates in mitochondria, it is typically used in rodents at very low doses (250 nmol/kg/day). However, no information is available on dosing in humans, including whether the pharmacokinetic and pharmacodynamic properties will allow safe or effective use. It is not currently available other than as an eye drop formulation in Russia and Europe.

What's the future?

SkQ1 is available in Russia as the eye drop Visomitin. Mitotech Pharma reported on its website in January, 2016 that it has started clinical development of Plastomitin, its systemic SkQ1 formulation, but did not mention what indication it will be pursuing. No new clinical trial is listed on clinicaltrials.gov. The company recently received an anti-aging patent in the US.

Search Terms:
Pubmed: SkQ1
Fight Aging!: SkQ1
Longecity: SkQ1

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If you have suggestions for drugs, drugs-in-development, supplements, nutraceuticals, or food/drink with neuroprotective properties that warrant in-depth reviews by ADDF's Aging and Alzheimer's Prevention Program, please contact INFO@alzdiscovery.org. To view our official ratings, visit Cognitive Vitality's Rating page.