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Epigenetic Treatment of Neurodegenerative Ophthalmic Disorders: An Eye Toward the Future

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Abstract
Eye disease is one of the primary medical conditions that requires attention and therapeutic intervention in aging populations worldwide. Further, the global burden of diabetes and obesity, along with heart disease, all lead to secondary manifestations of ophthalmic distress. Therefore, there is increased interest in developing innovative new approaches that target various mechanisms and sequelae driving conditions that result in adverse vision. The research challenge is even greater given that the terrain of eye diseases is difficult to landscape into a single therapeutic theme. This report addresses the burden of eye disease due to mitochondrial dysfunction, including antioxidant, autophagic, epigenetic, mitophagic, and other cellular processes that modulate the biomedical end result. In this light, we single out lipoic acid as a potent known natural activator of these pathways, along with alternative and potentially more effective conjugates, which together harness the necessary potency, specificity, and biodistribution parameters required for improved therapeutic outcomes.

Keywords: antioxidant; carnitine; lipoic acid; macular degeneration; mitochondria; retina

Introduction
Given the importance of vision and the number of age-related causes of vision loss (Table 1), including cataracts and macular degeneration,1–3 losing the ability to see is one of the greatest fears among the elderly, to some even more than death itself.4 The Ancient Greeks regarded vision to be the foremost means by which learning takes place. As early as the latter half of the 6th century Before the Common Era, the philosopher Alcmaeon of Croton5 believed that the eyes are connected directly to the brain.6 Two centuries later, by dissecting the human eye during autopsies on cadavers carried out in Alexandria, the Greek physician Herophilus of Chalcedon5 identified the optic nerves, tracing them directly to the brain.7 Today, the subject of the eye and the brain has in many places become...
required reading for students of life sciences. For example, Gregory's book, “Eye and Brain,” has been a classic since its first edition in 1966.

The human eye (Fig. 1) is a conveniently accessible, anatomically complex, highly specialized sensory organ with pharmacological properties that are largely organ-specific. These properties present unique opportunities to study effects of inflammation and infectious diseases in the eye, with relevance to the brain and central and autonomic nervous systems. The retina and optic nerve extend from the brain tissue. Similar to the brain, sheltered by the blood–brain barrier as an immune-privileged tissue, the eye is also an immunologically privileged site protected by the blood-retinal barrier. The retina is one of the highest metabolic oxygen-consuming tissues of the human body, exceeding even that of the brain, and its photoreceptors have the greatest density of mitochondria of all central nervous system (CNS) neurons. Mitochondria are intracellular organelles that carry multiple copies of a circular, maternally inherited, double-stranded DNA (mtDNA) comprised of ~16,500 base pairs in mammals. A principal role of mitochondria is to supply adenosine triphosphate (ATP), the bioenergy needed for cellular

Table 1. Major Causes of Vision Loss Worldwide

| Causes                          | Characteristics                       | Ranking as a cause of blindness in 2010 | Ranking as a cause of MSVI in 2010 |
|---------------------------------|---------------------------------------|----------------------------------------|-----------------------------------|
| Cataracts                       | Age-related, progressive              | 1                                      | 2                                 |
| Diabetic retinopathy            | Including sequelae                    | 4                                      | 5                                 |
| Glaucoma                        | All types                             | 2                                      | 4                                 |
| Macular degeneration            | Age-related, myopic, macular hole, and other forms | 3                                      | 3                                 |
| Refractive errors (uncorrected) | Includes aphakia                      | 2                                      | 1                                 |
| Trachoma                        |                                       | 5                                      | 6                                 |

Selected sources: Bourne et al., Tham et al., Wong et al., Aires et al.

MSVI, moderate to severe vision impairment.

FIG. 1. Basic structure of the human eye. (Adapted from: Artwork by Holly Fischer [CC BY 3.0 (http://creativecommons.org/licenses/by/3.0)], via Wikimedia Commons. Original File URL: https://upload.wikimedia.org/wikipedia/commons/d/d0/Three_Main_Layers_of_the_Eye.png).
maintenance and other essential biochemical processes. Importantly, when there is a buildup of damaged and/or dysfunctional mitochondria in the optic nerve, the nerve’s diminished capacity to produce enough ATP to supply its energy demands can result in severe visual impairment and lead to blindness.

Mitochondrial dysfunction is a prominent feature in the disease-progression mechanisms and pathways of a growing list of clinical disorders. Included among these are vision impairments such as cataracts, the most common cause of (preventable) blindness in the world, macular degeneration, diabetic retinopathy, and optic nerve diseases such as glaucoma. Glaucoma, an umbrella term for eye conditions that are caused by glaucomatous optic neuropathy, characterized by a progressive retinal ganglion cell loss and visual field damage, is the second leading cause of blindness worldwide. However, the ultimate form of mitochondrial dysfunction is expressed in the primary mitochondrial disorders and, with the brain and eye being insatiable consumers of ATP, it is not surprising that neuronal and/or ocular health are inevitable frontline casualties in these diseases.

In fact, (neuro-)ophthalmologic assessment is very much in order when mitochondrial disease is suspected (Table 2), even though significant clinical and genetic heterogeneity is evident in mtDNA mutation-driven disorders. In one study, 26 of 74 adult and pediatric patients with mitochondrial disease exhibited ophthalmologic abnormalities, and in another, 46 of 57 children and young adults with genetically verified mitochondrial disease had ophthalmologic findings. Signs of potential ocular involvement in mitochondrial disease may include hyperpigmentation of the retina, nystagmus, ptosis, ophthalmoplegia, optic atrophy, strabismus, and visual field defects. More extensive examination of the eye is required when the optic nerve itself is involved. Examples of the latter include autosomal dominant optic atrophy-related disorders and Leber’s hereditary optic neuropathy.

Although mitochondria in their production of ATP serve as the powerhouses of the cell, they also function as strategic platforms for intracellular signaling, as modulators of stem cell activity and cell death pathways, and as regulators of innate and adaptive immune responses to viral infections and other biological attacks. Indeed, a growing list of studies exposing the pivotal roles mitochondria play in immune-related pathways is fueling the characterization of mitochondria as the powerhouses of immunity. Thus, given these essential processes that mitochondria undertake in mitigating cell protection, survival, and function, they are attractive targets of opportunity for diagnostic, prognostic, and therapeutic indications, particularly in diseases of tissues with high energy needs. Breakthroughs in diagnosing and treating neurological disorders are in great need and the eye, being an accessible part of the brain, offers a clear window for us to begin to explore.

### Ocular Manifestations of Neurological Conditions and Disorders

For more than two millennia, physicians have looked to the eye as a sentinel indicator of disease. Abnormal avoidance of eye contact is an early risk-marker associated with autism. Several neurodegenerative conditions—Alzheimer’s disease (AD), inherited primary...
mitochondrial diseases, Parkinson’s disease, and multiple sclerosis among others—have manifestations in the eye. Indeed, ocular symptoms often precede conventional diagnosis of these conditions. In addition to when the eye itself is the target of infection, ocular symptoms are also common to viral diseases that affect the brain and CNS. Healthy mitochondrial function is necessary in upholding a competent innate immunity, the body’s frontline response against viral infections. Although these varied types of neurological and related conditions and disorders can have disparate root causes, they share in common mitochondrial dysfunction in their disease progression pathways. Consequently, the eye, not infrequently the first neuronal tissue affected by mitochondrial failure, offers itself as a model for energetic impairment in the CNS with direct implications for degenerative brain diseases (Table 3).

### Targeting Mitochondrial Dysfunction in Ocular Diseases

Many of the familiar features of aging seen in aged animals (including humans) correlate with epigenetic alterations that regulate transcription. Nutritional disequilibrium, epigenetic changes in gene expression, increased genomic instability, an erosion of telomeres, increased cellular senescence, and deregulated nutrient sensing are some of the age-related functional characteristics acting on or with each other that impact other hallmarks such as mitochondrial function and/or dysfunction and the degradation of an appropriate immune response.

Because mitochondria cannot be produced de novo, cells rely on the preservation of their healthy mitochondria from which mitochondrial biogenesis (the growth and division of pre-existing mitochondria) can occur. Mitophagy, a sub-form of autophagy, clears away damaged and/or dysfunctional mitochondria. Not surprisingly, given the irreplaceable nature of the mitochondrion and the indispensable roles mitochondria play in maintaining neuro-ocular health, mitoprotection has become an important target of pharmacological intervention—spawning an emerging pharmaceutical interest in developing “mitoprotectors,” and therapeutics for activating antioxidant and/or select mitophagic pathways. Mitophagy is critical for maintaining cellular function and preventing cell death.

#### α-Lipoic Acid and L-Carnitine

(α)-5-(1,2-dithiolan-3-yl)pentanoic acid, commonly known as α-lipoic acid (ALA, Fig. 2) and its reduced form (R)-6,8-bis(sulfanyl)octanoic acid, commonly referred to as dihydrolipoic acid (DHLA, Fig. 2) are enzymatically synthesized in mitochondria from octanoic acid. ALA and DHLA are naturally occurring cofactors for vital metabolic multi-enzyme complexes, including pyruvate dehydrogenase and glycerine decarboxylase. They possess powerful antioxidative effects and anti-inflammatory activity, instigate signal transduction modulatory pathways, and are well known to stimulate the expression of nerve growth factor and enhance conduction velocity of motor nerves.

### Table 3. Association of Vision Loss with Other Diseases

| Eye disease/indication | Cause/associated condition | Disease progression |
|------------------------|----------------------------|---------------------|
| Diabetic retinopathy   | Diabetes                   | Progressive degeneration leading to blindness |
| Macular degeneration   | Aging, complement dysregulation, oxidation, mitochondrial dysfunction | Progressive degeneration leading to legal blindness |
| Microvascular abnormalities | AD, diabetes, cardiovascular disease | Progressive degeneration leading to legal blindness |
| Optic nerve cupping, optic neuropathy | Glaucoma, ischemic optic neuropathies. Compressive optic neuropathies | |
| Pupillary abnormalities | AD, diabetes, optic nerve and CNS abnormalities | |
| Retinal neurodegeneration (thinning of RNFL) | AD, PD Several hundred genes isolated to day Deafness coupled with RP | Progressive blindness Progressive degeneration and deterioration |
| Usher syndrome         | AD, Alzheimer’s disease; PD, Parkinson’s disease; RNFL, retinal nerve fiber layer; RP, retinitis pigmentosa. |

AD, Alzheimer’s disease; PD, Parkinson’s disease; RNFL, retinal nerve fiber layer; RP, retinitis pigmentosa.
Additionally, ALA has significant histone deacetylase (HDAC) inhibitory activity.\textsuperscript{31,145} It is a potent activator of the nuclear factor erythroid 2-related factor 2 (Nrf2)/antioxidant response element (ARE) signaling pathway,\textsuperscript{28–32,162,163} which plays a central role in cellular defense against oxidative stress and the subsequent upregulation of ARE-dependent cytoprotective genes, including the heme oxygenase-1, catalase, and superoxide dismutase genes, without exhibiting cytotoxicity.\textsuperscript{164,165} Nrf2 is essential for supporting and maintaining normal mitochondrial function and structural integrity, particularly under conditions of cellular/neuronal stress inherent in neurodegenerative disorders.\textsuperscript{29} Oxidative stress is one of the main factors contributing to the pathogenesis of age-related macular degeneration (AMD),\textsuperscript{39,40,166–169} the most common cause of blindness in the elderly\textsuperscript{3,15,167,170,171} and the third-leading cause of blindness worldwide\textsuperscript{3} (Table 4).

Nrf2-mediated activity has been shown to decrease in aged rodents compared to younger pups, and in humans, in macrophages from older smokers in comparison with older nonsmokers, and in the affected brain regions of AD patients.\textsuperscript{166}

Although ALA reaps much attention in clinical therapy against a host of diseases susceptible to reactive oxygen species, including radiation exposure scenarios and heavy metal toxicity,\textsuperscript{28,175} its poor pharmacokinetic (PK) properties\textsuperscript{43,176–179} are a barrier to achieving sustainable therapeutic concentrations \textit{in vivo}.\textsuperscript{163,177,180,181} This PK deficit limits the range of ALA’s potential clinical indications. Nonetheless, ALA is an effective treatment option for diabetic neuropathy\textsuperscript{43,182} and possibly helpful in diabetic retinopathy,\textsuperscript{183} as outlined below.

In a clinical study evaluating oxidative stress, preretinal diabetic subjects who received oral treatment with ALA in combination with other antioxidants showed a
significant benefit in retinal elements—presumably due to a protective antioxidant effect on retinal cells (as determined by electroretinogram analysis). A protective antioxidant effect was also noted in a separate randomly assigned clinical trial involving 100 patients with dry AMD (50 patients given an oral administration of 0.2 g of ALA capsules daily for 3 months, and a control group of 50 patients receiving an oral administration of 1 g of vitamin C daily). Using the Chinese-Version Low Vision Quality of Life Questionnaire to assess vision-related quality of life, the ALA-treated group scored higher vs. the control group. In a study using a rat model of optic nerve crush injury, ALA administered intravenously (63 mg/kg) 1 day before or 1 day after the ONC injury was shown to have neuroprotective effects on retinal ganglion cells and a stronger prophylactic effect in the retina of the ONC-rats receiving ALA the day before the ONC injury. In a preliminary study with a higher species animal model (diabetic dogs) given ALA (2 mg/kg) orally, with ALA possibly acting as an antioxidant and/or as an aldose reductase inhibitor, the onset of glucose-sorbitol-induced cataracts was delayed, suggesting that the use of ALA should be studied for treating aldose-reductase-associated diabetic retinopathy in humans.

However, to more fully take advantage of ALA’s clinical potential as a drug candidate (particularly in ocular indications), its PK drawbacks must be resolved. With this in mind, mitochondria-targeting ALA-conjugated esters were conceived and synthesized. Chemical structures representing some of the conjugates that have been shown to have improved bioavailability and activity in vivo are shown in Figure 2.

Table 4. Characteristics of Age-Related Macular Degeneration

| Forms of AMD  | Degree of vision loss | Prevalence | Rate of progression |
|---------------|-----------------------|------------|--------------------|
| Early         | None                  | 80–90%     | Gradual/insidious over months/years | May progress to wet AMD |
| Intermediate  | Little or no vision loss; other symptoms may present such as decreased contrast sensitivity, and metamorphopsia. | 90–95% of all AMD | Can be sudden/profound over days/weeks if untreated; often follows dry AMD |
| Late or advanced | Minimal symptoms in early stages | 90–95% of all AMD | Gradual/insidious over months/years | May progress to wet AMD |

Selected sources: Fine et al., de Jong, Jager et al. 174

EV06 and PMX500FI (Fig. 2) are covalently linked esters of natural substrates (EV06: ALA and choline; PMX500FI: ALA and L-carnitine) that localize to and are operated on in mitochondria. A detailed and elegant study highlighting the anticancer properties of ALA (acting as a modulator of signal transduction and gene expression) inhibiting HDAC activity in human tumor cells was reported by van de Mark et al. In this study, choline was used as the vehicle (control), as it apparently has no noteworthy activity of its own in the assays used. However, choline is an essential nutrient and methyl donor required for epigenetic regulation and choline acetyltransferase (an enzyme that catalyzes the biosynthesis of the neurotransmitter, acetylcholine) is well-represented in ocular tissues of the human eye and in cholinergic cells of the brain and CNS.

L-Carnitine [L-(3R)-3-hydroxy-4-(trimethylammonio)butanoate], a natural compound primarily obtained from...
meat-containing foods in the diet and/or endogenously synthesized in the body,194 is a necessary nutrient of metabolic oxidation.195 It is required in the transport of medium-chain and long-chain fatty acids (acyl groups) between cell organelles and into the mitochondrial matrix where $\beta$-oxidation occurs, and in the removal of intermediate toxic products out of the mitochondria for excretion in urine.154,194,196,197 In combination with carnitine acyltransferases (a family of enzymes that catalyze the reversible transfer of acyl groups between coenzyme A [CoA] and L-carnitine), acyl-carnitine esters are converted into acyl-CoA esters, the active acyl substrate operated on by the mitochondrial enzymes in $\beta$-oxidation; in the export of excess acetyl groups from the mitochondria; and in acetylation reactions that regulate gene transcription and enzyme activity.194 L-carnitine has also been shown to confer protection in the prevention of radiation-induced brain and retinal damages.198,199

**Nrf2, and Epigenetic Attributes of ALA, L-Carnitine, and Their Conjugated Esters**

Retinal diseases and/or damages leading to a substantial loss of retinal neurons can result in visual impairment that may be permanent. The adult mammalian retina has little capacity for regeneration,200,201 and as noted previously, unmitigated oxidative stresses in ocular tissues can cause irreversible harm to the eye. The Nrf2-Kelch-like ECH-associated protein 1 (Keap1) assembly is one of the main cellular defense systems against oxidative stresses.110,169,202 Nrf2 is a key nuclear transcriptional inducer. It couples with ARE in the DNA promoter and synchronizes the transcription of a large number of antioxidant genes, including glutathione-S transferase, glutathione reductase, and thioredoxin reductase.110 Notably, the Nrf2/ARE/Keap1 signaling pathway regulates anti-inflammatory gene expression and inhibits the progression of inflammation.203 Relevant to this discussion, ALA and L-carnitine, separately and/or as a conjugate ester (PMX500FI), are HDAC inhibitors that independently may act to prolong epigenetic gene expression.31

Nrf2 production (Nfe2l2 gene expression) has been demonstrated (in animals) to decline progressively with age,141,166 and this may in part account for the retinopathies,45 including macular degeneration, presenting as age-related diseases of the eye.204–206 An imbalance in oxidative stress and antioxidant defense mechanisms contributes to the pathogenesis of both inherited and acquired corneal pathologies23,24 and to the development of ischemic retinopathies such as diabetic retinopathy and retinopathy of prematurity.207 A study designed to model retinopathies in mice showed that Nrf2 activation reduced the vision-threatening features of oxygen-induced retinopathy, namely vasoobliteration, neovascularization, and vascular leakage, with potential therapeutic utility.207

Interestingly, activation of the Nrf2 cell defense pathway can also be influenced by diet.208–214 Deregulated nutrient sensing is one of the hallmarks of aging112,114 and numerous studies link elevated levels of oxidative stress and inflammatory changes in various tissues and organs to a dysbiotic shift in the gut microbiota.90,215 Kugadas et al.216 suggest that pathogenic bacteria in the gut may affect ocular disease susceptibility, and provide experimental evidence for the existence of a gut-eye axis of immune regulation. A study by Rowan et al.217 discovered that metabolites and microbiota, acting together within a gut-retina axis, appear to protect against diet- and age-induced AMD features—implying that a simple dietary intervention may have complementary use in the treatment of patients with AMD.218,219 Indeed, metabolomics is an emerging and promising laboratory testing technique for identifying blood profiles associated with AMD across all its stages and severity.220 Microbiome research in general is an aggressive field of study and although the gut microbiome has captured most of the attention,215 the microbiota on the surface of the human eye (ocular microbiome) is drawing increasing interest as a unique and immunoprotective commensal ecosystem.32,216,221–224

**Concluding Remarks**

As should be clear at this point, eye disease is a primary medical condition that often requires immediate attention and therapeutic intervention in ageing populations worldwide, not to mention pediatric and young adult patients. Exacerbating the problem is the increasing global burden of diabetes and obesity, along with heart disease, which all lead to significant secondary and tertiary manifestations of ophthalmic distress. Even less serious challenges such as managing dysfunctional tear syndrome continue to frustrate greatly both patients and eye care professionals.225,226 Therefore, increased interest is manifold in developing innovative new approaches that target various mechanisms and sequelae driving conditions that result in adverse vision. The research and development challenges are even greater given that the varied and extensive terrain of eye diseases is difficult to landscape into a single or even two or three therapeutic themes, although some would say that all roads may ultimately lead to mitochondria.
Thus, in this report, we have attempted to address the burden of eye disease due to mitochondrial dysfunction, including antioxidant, autophagic, epigenetic, mitophagic, and other essential cellular processes that modulate the biomedical end result. In such a light, it is appropriate to single out lipoic acid as a potent known natural activator of these pathways, along with alternative and potentially more effective carnitine conjugates, which together we anticipate could harness the necessary and complete profile of potency, specificity, and biodistribution parameters that are required for improved therapeutic outcomes.

In particular, Nrf2 is an important endogenous protective factor against oxidative stress and essential for supporting and maintaining normal mitochondrial function, especially in neuroretinal and other high energy-demanding tissues. The clinical development of drugs that modulate Nrf2 expression is vigorously being researched as a neuroprotective strategy for treating conditions of oxidative stress, including age-related cataracts and AMD.24,110,169,202,227–233

Eye disease is reaching epidemic proportions worldwide.234 As yet one more example, it is estimated that the incidence of glaucoma will exceed 100 million cases by 2040,235–238 and most of the people affected will reside in Asia and Africa.2 These healthcare juggernauts are due to primary causes as well as secondary manifestations resulting from metabolic distress in the eye, brain, and elsewhere in the body where energy demanding cell types are resident—again, think mitochondria.239 Ageing populations add to the burden. The revival of interest in developing novel eye disease therapies237–241 is consequently no surprise. We hope that our review convinces even more researchers to join the search for the next generation of safe and effective ophthalmic medicines.

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Authors’ Contributions
All authors contributed to the writing of this article and agreed to its final content.

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K.S. owns shares in PhenoMatriX, Inc. K.K. and W.H.M. consult with and/or serve on the boards of various biotechnology and pharmaceutical companies from time to time, where they may receive compensation and/or stock options, and they receive compensation from ShangPharma Innovation, Inc., a healthcare venture capital firm.

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Abbreviations Used

AD = Alzheimer’s disease
ALA = α-lipoic acid
AMD = age-related macular degeneration
ARE = antioxidant response element
ATP = adenosine triphosphate
CNS = central nervous system
CoA = coenzyme A
DHLA = dihydrolipoic acid
EVO6 = lipoylcholine chloride
HDAC = histone deacetylase
Keap1 = Nrf2-Kelch-like ECH-associated protein 1
KSS = Kearns-Sayre syndrome
MC = mitotic catastrophe
MNGIE = mitochondrial neurogastrointestinal encephalomyopathy
MSVI = moderate to severe vision impairment
Nrf2 = nuclear factor erythroid 2-related factor 2
PD = Parkinson’s disease
PEO = progressive external ophthalmoplegia
PK = pharmacokinetic
RNFL = retinal nerve fiber layer
RPE = retinal pigment epithelial

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