VISION PAPER™ No. 9

From the Retina to the Brain: Extending the OCT-Guided Biological Intervention Framework of VISION PAPER™ No. 6 to Alzheimer's Disease

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VISION PAPER™, Interdisciplinary Platform for Health, Longevity and Scientific Dialogue

Hypothesis paper • 2026

Preamble

This paper builds on the ideas formulated in VISION PAPER™ No. 6. No. 6 established the concept of OCT-guided biological intervention using the example of glaucoma: SLT not merely as an intraocular pressure-lowering procedure, but as an intervention targeting monocytes/macrophages, cytokine signalling and mitochondrial resilience, documented through longitudinal OCT observations following SLT combined with resveratrol-based metabolic support [1].

No. 9 extends this perspective to Alzheimer's disease. The central question is no longer only whether a retinal intervention supports the survival of retinal ganglion cells, but whether the underlying mechanism - the modulation of macrophage/microglia polarisation - can act beyond the retina on the brain. The retina is not an isolated organ. Embryologically, neurochemically and immunologically, it is upstream brain tissue. If SLT deactivates retinal microglia and if metabolic support promotes M2 polarisation, then the question of cerebral relevance is not speculative but the logical next question.

This paper is a hypothesis. It contains no new empirical data on cognitive endpoints. It formulates a testable extension of the ideas begun in No. 6.

1. Starting Point: What VISION PAPER™ No. 6 Established

No. 6 documented a recurring pattern in longitudinal OCT observations: RNFL thinning → intervention (SLT + resveratrol) → structural response → renewed thinning → renewed intervention → renewed response [1]. This finding proves neither regeneration nor causality. It is a clinical observation that generates questions.

Two conceptual elements from No. 6 are decisive for the extension to Alzheimer's disease:

First: SLT was not conceived as purely physical pressure lowering, but as a biological intervention influencing monocytes/macrophages, cytokine signalling and extracellular matrix remodelling [1]. This conceptualisation is the bridge to neuroinflammation.

Second: Metabolic support with resveratrol was conceived via SIRT1/AMPK → PGC-1α and mTOR inhibition, with the aim of mitochondrial energy and autophagy [1]. The same metabolic pathway is relevant for microglial polarisation in the brain [6].

2. The Retina as a Window to Cerebral Pathology: Evidence and Limits

The assumption that retinal changes mirror cerebral processes is not new, but it is empirically grounded. RNFL thinning is discussed as an early sign of neurodegenerative diseases including glaucoma, Alzheimer's disease and dementia [5]. In No. 6, this observation was used for glaucoma. For Alzheimer's disease, the question is posed differently: not whether the retina mirrors the brain state, but whether an intervention in the retina can influence the brain state.

A clear demarcation is necessary here. The retina is an accessible window. It is not a therapeutic access route to the brain in the pharmacological sense. The hypothesis of this paper is not that

SLT overcomes the blood-brain barrier or acts directly on the hippocampus or cortex. The hypothesis is that the immunomodulatory mechanism observed in the retina could act at a systemic level that also reaches the brain - mediated via circulating monocytes and the shared NF-κB signalling axis.

The central mechanistic uncertainty must be named here: Whether a local ocular stimulus - particularly within the immune-privileged compartment of the eye - is sufficient to modulate systemically relevant monocyte populations such that they alter microglial polarisation in the CNS is currently unproven and theoretically questionable. The blood-retina barrier limits the spread of local cytokine signals. This gap is the greatest weakness of the cascade formulated in Section 6 and is explicitly addressed as an open question in Section 7.

3. SLT and Microglia: The Retinal Evidence - and Its Limits

The most direct human evidence for laser-induced microglial modulation in the retina comes from a prospective observational study in diabetic macular oedema. After subthreshold micropulse laser (SMPL), aqueous humour levels of MIP-1α, RANTES, FasL and VEGF decreased significantly [2]. The authors concluded that these cytokines are "produced mainly by retinal microglia" and that SMPL "acts by deactivating microglial cells" [2].

Important limitation: This study investigated SMPL at the macula - not SLT at the trabecular meshwork. SLT (532 nm, nanosecond-pulsed) targets the trabecular meshwork in the anterior chamber angle anatomically, not the neurosensory retina. A critical objection is therefore: a laser at the chamber angle does not automatically produce the same microglial deactivation in the retina as a macular micropulse laser.

The bridge between the two procedures is the shared principle of sub-destructive photothermolysis/photostimulation, which alters cytokine cascades in the aqueous humour [2]. However, direct evidence of retinal microglial deactivation by SLT at the trabecular meshwork is still lacking. This study was not conducted in glaucoma or AMD, and it did not examine the brain. But it provides the molecular proof that a laser intervention in the retina can reduce microglial activation without destroying tissue - provided the laser reaches the neurosensory retina. That is the starting point, not the proof.

4. Photobiomodulation and Cerebral Microglia: The Bridge - with a Physical Caveat

If retinal microglia can be deactivated by laser, the question arises whether comparable modulation is also possible in the central nervous system. Photobiomodulation (PBM) - related to SLT in the principle of light-tissue interaction, but with a different wavelength (typically 810-1070 nm near-infrared) and markedly different tissue penetration - provides the decisive evidence here.

A study in 5xFAD mice showed that 1070-nm light (10 Hz, 4 J/cm²) shifts microglia from an M1 to an M2 phenotype. The M2 microglia secreted exosomes carrying miR-7670-3p, which reduced endoplasmic reticulum stress via ATF6 inhibition, dampened neuroinflammation and protected dendritic spines in the cortex and hippocampus - with measurable improvement in cognition

[4]. A review in Alzheimer's Research & Therapy confirms: PBM regulates microglial polarisation, promotes Aβ clearance and improves mitochondrial function in AD models [7].

Physical contextualisation: The transition from SLT (532 nm, chamber angle, nanosecond pulses) to transcranial PBM (1070 nm, tissue penetration into the cortex, continuous or pulsed irradiation) is physically a major leap. The PBM data serve here as proof of concept for the fundamental light sensitivity of microglia - not as evidence that SLT exerts the same physical mechanism of action in the brain. These data come from animal models. They prove nothing for humans. But they show that near-infrared light can reach and polarise cerebral microglia - a mechanism distinct from that of SLT at the eye.

Weighting of the strands: While SLT and PBM substantiate the light-microglia axis and establish the retina as a local test field and readout, the systemic-cerebral effect lies primarily with the oral components. The following consideration of resveratrol and TMG should therefore not be read as "support" for the laser intervention, but as an independent, systemically active strand - the retina is the place where its effect becomes visible, not the place where it originates.

5. Resveratrol and TMG: Metabolic and Inflammatory Convergence

No. 6 conceived resveratrol via SIRT1/AMPK → PGC-1α and mTOR inhibition [1]. This conceptualisation is relevant to Alzheimer's disease for two reasons.

First: PGC-1α is not only a regulator of mitochondrial biogenesis. PGC-1α is a node of microglial polarisation. Resveratrol regulates M1/M2 polarisation of microglia via PGC-1α [6]. The metabolic pathway described in No. 6 is thus directly coupled to the polarisation mechanism relevant to Alzheimer's pathology.

Autophagy in this context is not merely a cellular quality-control programme. It is a clearance mechanism for aggregated proteins - including Aβ - and thus directly coupled to Alzheimer's pathology. Resveratrol-induced autophagy via AMPK/mTOR is, in this sense, not only metabolic support but a potential clearance contribution [6].

Second: The addition of trimethylglycine (TMG, betaine) introduces a component not included in No. 6, whose evidence for microglial polarisation is more direct than that of resveratrol. In N9 microglial cells, betaine dose-dependently reduced TNF-α, IL-1β, IL-6 and NO, reduced iNOS and CD16/32 (M1 markers), increased CD206 and arginase-1 (M2 markers) and inhibited the TLR4/MyD88/NF-κB signalling pathway [3]. Betaine "penetrates the blood-brain barrier" and shows high distribution to the hippocampus [3].

The combination is mechanistically complementary: TMG acts on the TLR4/NF-κB node that initiates pro-inflammatory polarisation. Resveratrol acts on SIRT1/AMPK/PGC-1α, which provides the metabolic capacity for M2 polarisation. Both converge on inhibition of NF-κB and promotion of M2 polarisation, but via different upstream nodes.

Bioavailability and first-pass metabolism: Resveratrol is subject to extensive hepatic first-pass metabolism, which substantially limits its systemic availability. The formulation used in Health Pro addresses this via two principles: first, combination with micronutrients (vitamin C, B vitamins, zinc, copper) that act as cofactors of antioxidant and inflammation-modulating enzymes and provide the organism's metabolic capacity for utilising the active compounds.

Second, the principle of metabolic diversion: the simultaneous supply of multiple substrates can distribute hepatic metabolising capacity and thereby favour the unchanged passage of resveratrol into the systemic circulation. This is not a pharmacological formulation in the strict sense, but a strategic combination that responds to the reality of first-pass metabolism. Whether and to what extent this strategy increases cerebral availability is an open, measurable question - it is part of ongoing formulation development and not the subject of this paper.

6. The Hypothesis: A Shared Axis

The hypothesis formulated in this paper is:

SLT-induced retinal microglial deactivation and oral supplementation with TMG plus resveratrol could act synergistically on retinal and cerebral macrophages/microglia via shared NF-κB and metabolic pathways. The retina thereby serves as an accessible readout for a process that could be systemically and centrally relevant.

The postulated cascade - with explicit identification of uncertainties:

1. Retinal local: SLT deactivates M1-polarised microglia, lowers MIP-1α, RANTES and VEGF [2] - direct human evidence for SLT at the trabecular meshwork is lacking; evidence derives from SMPL at the macula.
2. Metabolic: Resveratrol activates AMPK/PGC-1α, promotes autophagy and mitochondrial biogenesis [6].
3. Inflammatory: TMG inhibits TLR4/NF-κB and NLRP3, shifts microglia toward M2 [3].
4. Systemic-central: Shared NF-κB inhibition could reach cerebral microglia via circulating monocytes and the blood-brain barrier penetration of TMG [3] - whether a local ocular stimulus is sufficient to modulate systemically relevant monocyte populations is open (see Section 2).
5. Readout: OCT parameters (RNFL, macular thickness) could serve as longitudinal biological feedback - not as proof of cerebral effects, but as an indicator of the system's responsiveness.

Conceptual clarification: The systemic-cerebral work is performed primarily by TMG and resveratrol. SLT and OCT constitute the local retinal test field and the diagnostic readout. The hypothesis is not that the laser reaches the brain, but that the oral metabolic-inflammatory intervention could have cerebral relevance, while the retina serves as a measurable window.

7. What This Hypothesis Does Not Claim

- It does not claim that SLT treats Alzheimer's disease. The SLT data derive from DME eyes (SMPL), not from AMD or AD populations. The PBM data derive from mice.
- It does not claim that the blood-brain barrier is "overcome." TMG penetrates the blood-brain barrier [3]. SLT does not. The hypothesis is not that the laser reaches the brain, but that the systemic immunomodulatory effect of the combined intervention could have cerebral relevance.
- It does not claim that a local ocular stimulus is sufficient to modulate systemically relevant monocyte populations. This is the greatest mechanistic uncertainty of the postulated

cascade. The eye is an immune-privileged compartment; the blood-retina barrier limits the spread of local cytokine signals. Whether SLT at the trabecular meshwork generates a systemic immune signature strong enough to reprogramme peripherally circulating monocytes is currently unproven. This question is experimentally testable (see Section 8).
- It does not claim that AMD and Alzheimer's disease are the same disease. The epidemiological association is statistically present but variable. The shared axis is immune polarisation, not aetiology.
- It does not claim that clinical efficacy has been demonstrated. No study has investigated SLT plus TMG/resveratrol in Alzheimer's patients with cognitive endpoints. This hypothesis is a starting point for prospective research, not a therapeutic protocol.

8. Testable Predictions

If the hypothesis holds, prospective studies should show the following patterns:

- Systemic immunomodulation: Patients receiving SLT plus TMG/resveratrol show a reduction in systemic inflammatory markers (hs-CRP, IL-6) compared with a control group - this directly tests the mechanistic gap identified in Sections 2 and 7.
- Retinal stability: Retinal OCT parameters (RNFL, macular thickness) stabilise over a longer period than with SLT alone.
- Cognitive coupling: Long-term observation shows a slowed cognitive decline - provided retinal and cerebral immunomodulation are coupled.

Study population: A cohort of glaucoma patients (or patients with ocular hypertension) who already have an indication for SLT and in whom mild cognitive impairment (MCI) is documented would be the obvious choice. This avoids the logical break of using SLT in AMD populations, for whom SLT is not a standard therapy. Alternatively, an AMD cohort would be conceivable if the intervention is argued primarily via TMG/resveratrol and SLT serves only as a local readout stimulus - this would, however, require explicit justification.

If these patterns fail to appear, the hypothesis is to be rejected. That is the purpose of a Vision Paper: to formulate a testable framework, not to assert a truth.

9. Conclusion

VISION PAPER™ No. 6 asked: "How do we help the neuron survive?" No. 9 extends the question: Could the mechanism that helps the retinal neuron also help the cerebral neuron - not through direct access, but through a shared immunological axis?

The answer is unknown. But the question is precise enough to be investigated. The retina is accessible. The microglia are the same cells. The NF-κB axis is the same. What is missing are prospective data testing the bridge - and the critical examination of whether a local ocular stimulus can become systemically relevant.

This paper formulates the bridge and names its weakest point. The next steps are clinical.

Conflicts of Interest: The author is founder and CEO of PAULIG EYE & HEALTH and develops formulations in the field of mitochondrial and metabolic support. The compounds discussed in

this paper (resveratrol, TMG) are part of this formulation development; the bioavailability strategy of Health Pro is the subject of this development.

Funding: No external funding.

Acknowledgements: This contribution builds on the ideas formulated in VISION PAPER™ No. 6 and would not be conceivable without the longitudinal clinical observation documented there.

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16.11.2026

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