VISION PAPER™ No. 6

Beyond Pressure Reduction

Rethinking Glaucoma Therapy Through Cellular Protection and Metabolic Resilience

6.1 Lowering Pressure Is Essential — But Is It Enough?

For decades, glaucoma therapy has been built around one central therapeutic target: **intraocular pressure (IOP).**

And for good reason.

Lowering IOP remains the only therapeutic intervention that has consistently been shown to reduce the risk of glaucomatous progression and preserve visual function. This applies even to normal-tension glaucoma, where pressure values are already within what has traditionally been considered the normal range.

The landmark Collaborative Normal-Tension Glaucoma Study demonstrated that lowering IOP by approximately 30% significantly reduced the likelihood of progression in patients with normal-tension glaucoma.

This finding fundamentally changed our understanding of the disease: even a pressure that is statistically "normal" may still be biologically too high for an individual optic nerve.

But it also revealed something equally important.

Pressure reduction does not explain everything.

Some patients continue to lose retinal nerve fibre layer, retinal ganglion cells and visual function despite apparently well-controlled intraocular pressure. Conversely, some patients with normal-tension glaucoma remain remarkably stable for years.

This heterogeneity raises a fundamental question:

If pressure were the entire disease, why does lowering pressure not protect every patient?

Perhaps the answer lies in distinguishing between a **risk factor** and the **biological vulnerability of the tissue exposed to that risk factor**.

The same mechanical load may be tolerated by one optic nerve and not by another.

The same intraocular pressure may therefore represent very different biological stresses depending on the structural, vascular and metabolic resilience of the individual eye.

This becomes particularly relevant in normal-tension glaucoma.

Here, the therapeutic paradox becomes visible: we lower a pressure that was never elevated in the conventional sense because doing so reduces one component of stress on an already vulnerable system.

That is rational and evidence-based.

But it may not be sufficient.

Normal-Tension Glaucoma Is No Longer a Marginal Phenomenon

Normal-tension glaucoma was once regarded primarily as an unusual subtype of primary open-angle glaucoma.

Epidemiological evidence increasingly challenges this perception.

While reported proportions of normal-tension glaucoma among primary open-angle glaucoma are substantially lower in Western populations, studies from East Asia have repeatedly reported dramatically higher proportions. In several Asian populations, the majority of patients diagnosed with primary open-angle glaucoma have intraocular pressure within the statistically normal range.

In Japan, landmark population-based data have suggested proportions exceeding 90%.

This observation deserves more than epidemiological attention.

If glaucomatous optic neuropathy can so frequently develop without conventionally elevated intraocular pressure, elevated pressure cannot be considered a universal explanation for the disease.

It remains an important and modifiable risk factor.

But risk factor and disease mechanism are not synonymous.

The Diagnostic Blind Spot: Do We Find What We Look For?

The striking prevalence of normal-tension glaucoma in East Asian populations is commonly interpreted as evidence of geographical or biological differences.

This may indeed be part of the explanation.

Genetic background, myopia and axial length, vascular regulation and other population-specific factors may contribute to the particularly high prevalence reported in Japan and other Asian countries.

But there is another possibility that deserves greater attention:

Do we find what we actively look for?

Normal-tension glaucoma is inherently more difficult to detect within a diagnostic system historically centred on elevated intraocular pressure.

When pressure is elevated, it immediately raises suspicion. Further examination follows.

When pressure is normal, however, this diagnostic trigger disappears.

The consequence may be substantial underdiagnosis.

European data support this concern.

Population-based screening studies have demonstrated that a considerable proportion of glaucoma remains undiagnosed. More importantly, studies comparing systematic screening with routine clinical detection have found markedly higher proportions of normal-tension glaucoma when populations are actively examined for glaucomatous damage rather than selected primarily through elevated intraocular pressure.

In one European screening study, **52.9% of glaucoma detected through systematic screening was classified as normal-tension glaucoma, compared with only 13.5% among patients identified through routine clinical pathways.**

More recent European population data reinforce the broader diagnostic problem. A large 2025 analysis comprising **55,415 participants from 14 population-based European studies found that 56.4% of individuals identified as having glaucoma had previously been undiagnosed.**

These observations raise an important epidemiological question.

The lower reported prevalence of normal-tension glaucoma in Europe compared with East Asia may reflect genuine biological differences.

But it may also partly reflect differences in how intensively we search for glaucoma when intraocular pressure is normal.

Epidemiological statistics do not only describe biology.

They also reflect **diagnostic behaviour**.

A disease phenotype that is systematically searched for will be detected more frequently than one that remains outside the primary diagnostic focus.

The extraordinarily high proportion of normal-tension glaucoma reported in Japan should therefore not simply lead us to conclude that normal-tension glaucoma is predominantly an Asian phenomenon.

It should provoke another question:

What would the epidemiology of glaucoma in Europe look like if we searched as systematically for neurodegeneration at normal intraocular pressure?

From Measuring Pressure to Detecting Neurodegeneration

This question becomes particularly important in the era of optical coherence tomography.

We are no longer dependent on elevated pressure or advanced visual field loss to alert us to disease.

Structural neuronal loss can increasingly be identified and followed through careful assessment of the optic nerve, retinal nerve fibre layer and ganglion cell structures before substantial functional impairment becomes apparent.

If structural damage is not actively sought, however, a patient with normal intraocular pressure may remain invisible to a pressure-centred diagnostic pathway for years.

The diagnostic paradigm can therefore change:

from searching primarily for elevated pressure to searching for early neurodegeneration.

And if the way we search changes, the epidemiology we observe may change with it.

From Pressure Control to Biological Resilience

The retinal ganglion cell does not live in isolation from the rest of human biology.

Its survival depends on energy production, mitochondrial integrity, axonal transport, vascular supply, oxygen delivery, redox balance, inflammatory regulation and the capacity to respond to cellular stress.

A neuron with sufficient energetic reserve may tolerate a certain degree of mechanical or vascular stress.

A metabolically compromised neuron may not.

This suggests that glaucoma therapy may need to evolve from a predominantly pressure-centred model toward a broader concept:

Reduce the stress — and strengthen the cell.

These are not competing strategies.

IOP reduction remains essential.

The question is whether the next generation of glaucoma therapy should complement it by identifying and addressing the factors that determine why one retinal ganglion cell survives while another degenerates.

Instead of asking only:

“How much further can we lower the pressure?”

we may also need to ask:

“What is making this optic nerve vulnerable?”

And perhaps even more fundamentally:

“Why does an optic nerve degenerate when intraocular pressure was never pathologically elevated in the first place?”

These questions open a much wider therapeutic landscape.

They direct attention toward ocular perfusion and vascular autoregulation. Toward mitochondrial energy production and oxidative stress. Toward neuroinflammation, metabolic resilience and systemic factors that may influence the biological environment of the optic nerve.

Not all of these pathways have yet translated into established clinical therapies. Neuroprotective strategies remain an active field of research, and current glaucoma guidelines appropriately continue to regard IOP reduction as the only intervention proven to preserve visual function.

But the absence of an established therapy does not mean that the underlying biology should be ignored.

It means that the next therapeutic frontier has not yet been fully defined.

The history of glaucoma treatment has taught us how to reduce pressure.

The next challenge may be to understand **how to preserve the neuron that pressure reduction is intended to protect.**

The future of glaucoma therapy may therefore not be a choice between pressure reduction and neuroprotection.

It may be their integration.

Pressure remains a modifiable stressor.

But cellular resilience may determine how successfully the optic nerve survives that stress.

And if that is true, the therapeutic goal of the future will extend beyond achieving a target pressure.

It will be to create the biological conditions in which retinal ganglion cells have the greatest possible chance to survive.

6.2 SLT: More Than Pressure Reduction?

Selective laser trabeculoplasty is generally classified as a pressure-lowering treatment.

Clinically, this is correct.

Biologically, however, it may be an incomplete description.

SLT does not simply create a mechanical opening through which aqueous humor can escape. Unlike older concepts of laser trabeculoplasty based predominantly on structural or thermal effects, SLT appears to initiate a complex biological response within the trabecular meshwork.

This distinction may be more important than we have traditionally assumed.

The Trabecular Meshwork Is Living Tissue

The trabecular meshwork is not merely a passive drainage filter.

It is a metabolically active and dynamically regulated tissue involved in maintaining aqueous humor outflow and intraocular pressure homeostasis.

Its endothelial-like cells interact with extracellular matrix, respond to mechanical and biochemical signals and possess phagocytic capacity.

With aging and glaucoma, this system can change.

Trabecular cellularity may decline. Extracellular matrix turnover may become disturbed. Tissue stiffness can increase. Cellular stress, fibrosis and impaired phagocytic function may progressively alter the resistance of the conventional outflow pathway.

From this perspective, glaucoma treatment should not only ask how aqueous humor can bypass resistance.

It should also ask whether the function of the tissue creating that resistance can be restored.

SLT Initiates a Biological Response

Experimental evidence increasingly supports such a concept.

Following SLT, monocytes are recruited into the trabecular meshwork. Experimental studies have demonstrated a several-fold increase in monocyte recruitment following laser treatment.

These monocytes and macrophages are not passive bystanders.

They appear to participate in aqueous outflow regulation.

Experimental studies have demonstrated that monocytes and monocyte-derived factors can increase outflow facility and alter the conductivity of Schlemm's canal endothelial cells.

SLT also induces cytokine signalling within the conventional outflow pathway.

This signalling may influence extracellular matrix remodelling, cellular permeability and communication between trabecular meshwork cells and Schlemm's canal endothelial cells.

The pressure-lowering effect of SLT may therefore emerge from a coordinated biological response rather than from a purely mechanical laser effect.

This changes the way we can think about the procedure.

From Laser Treatment to Tissue Response

If SLT recruits immune cells, modifies cytokine signalling and stimulates extracellular matrix remodelling, then its therapeutic effect may be understood as a form of **controlled biological activation of the outflow system**.

The innate immune system may play a particularly interesting role.

Macrophages are among the body's fundamental mechanisms for recognising, processing and removing damaged cellular material.

Within the trabecular meshwork, such activity may contribute to restoring a more functional environment for aqueous outflow.

Recent experimental work adds another dimension.

In human trabecular meshwork cells exposed to glucocorticoids, SLT has been shown to reduce fibrotic and myofibroblast-like changes while partially restoring impaired phagocytosis and cellular proliferation.

These findings do not prove that SLT regenerates the trabecular meshwork in patients.

But they reinforce an important principle:

SLT can influence cellular behaviour, not only intraocular pressure.

From Clinical Observation to a Testable Hypothesis

Our clinical experience with selective laser trabeculoplasty began in 2007.

Over time, and particularly in patients with normal-tension glaucoma, an observation increasingly challenged a purely pressure-centred interpretation of SLT.

The question was no longer simply whether intraocular pressure decreased after treatment.

We began to ask whether the **biological response induced within the trabecular meshwork itself** might be therapeutically relevant.

This question became particularly important during long-term structural follow-up using optical coherence tomography.

In patients in whom retinal nerve fibre layer loss could be followed over time, the relationship between intraocular pressure and structural progression was not always straightforward.

Some eyes continued to deteriorate despite apparently acceptable pressure values, while others appeared structurally more stable than pressure measurements alone would have predicted.

From these observations emerged a working hypothesis:

Could SLT influence the biological environment of the eye in ways that are not completely captured by measuring intraocular pressure alone?

One potential mechanism attracted particular attention: activation and recruitment of monocytes and macrophages within the trabecular meshwork.

The concept was biologically compelling.

Macrophages are not simply inflammatory cells. They are fundamental components of tissue surveillance, clearance and repair. Their capacity to phagocytose cellular debris and participate in extracellular matrix turnover suggested that their recruitment after SLT might contribute to restoring a more functional trabecular environment.

This led us to consider SLT increasingly as a potential form of **biological activation and tissue cleaning**, rather than exclusively as a pressure-lowering laser procedure.

Importantly, this interpretation initially arose from clinical observation and biological reasoning.

Subsequent and evolving experimental research has increasingly provided mechanistic support for parts of this concept.

Studies have demonstrated a several-fold recruitment of monocytes into the trabecular meshwork following SLT. Monocytes and macrophages have been shown experimentally to increase aqueous outflow facility and alter Schlemm's canal endothelial conductivity.

Further research has expanded this biological model toward cytokine signalling, extracellular matrix remodelling, phagocytic function and restoration of trabecular cellular behaviour.

These findings do not prove that SLT directly protects retinal ganglion cells.

Nor do they establish that macrophage activation in the anterior chamber independently prevents RNFL loss.

That remains our hypothesis — and an important distinction.

But the convergence between long-term clinical observation and increasingly detailed experimental evidence raises a question that deserves prospective investigation:

Could SLT Exert Disease-Modifying Effects That Are Not Adequately Described by the Magnitude of IOP Reduction Alone?

If so, the relevant endpoint for future studies should not be pressure alone.

It should include longitudinal structural outcomes:

RNFL thickness. Ganglion cell integrity. Rate of progression. And ultimately, preservation of neuronal function.

This distinction is particularly important in normal-tension glaucoma, where the pressure reduction achieved by SLT may be numerically modest precisely because baseline pressure is already low.

If treatment success is defined exclusively by millimetres of mercury, a biologically meaningful response could potentially remain invisible.

The hypothesis therefore does not replace the established pressure-lowering mechanism of SLT.

It extends the question.

Perhaps the most important effect of SLT is not only what happens to pressure — but what happens to the tissue after the laser pulse has disappeared.

Experimental Models and Human Clinical Observation

Some of the most exciting developments in retinal ganglion cell protection and regeneration currently originate from experimental research.

Work at Harvard Medical School and Mass Eye and Ear has demonstrated in mouse models that retinal ganglion cells may retain a previously underestimated capacity for biological restoration.

Experimental epigenetic reprogramming using Oct4, Sox2 and Klf4 has promoted axonal regeneration and restored visual function in models of optic nerve injury, ageing and glaucoma.

These findings are remarkable.

They challenge the long-standing assumption that neuronal damage in the adult visual system is necessarily irreversible and open an entirely new field of regenerative ophthalmology.

But they also illustrate an important principle in translational medicine:

Experimental evidence and human clinical observation should not compete with each other. They should inform each other.

Animal models allow mechanisms to be isolated, manipulated and investigated with a precision that is often impossible in humans.

Clinical medicine provides something different.

It allows us to observe what happens in the complex biological system of the human patient — repeatedly, longitudinally and sometimes over many years.

In our own clinical work, structural OCT and RNFL observations following SLT in patients with normal-tension glaucoma have accumulated over almost a decade.

These observations were not generated in an experimental mouse model.

They arose in human eyes under real clinical conditions.

They do not constitute randomized proof that SLT induces retinal ganglion cell regeneration or IOP-independent neuroprotection.

We should not claim that they do.

But neither should long-term clinical observations in humans be dismissed simply because the underlying mechanism has not yet been fully demonstrated experimentally.

Clinical observation has historically preceded mechanistic explanation in many areas of medicine.

The scientifically appropriate response to an unexpected and reproducible clinical observation is therefore neither premature certainty nor premature rejection.

It is investigation.

If repeated longitudinal OCT observations suggest structural stabilization — or potentially changes that cannot be adequately explained by pressure reduction alone — these findings should generate prospective hypotheses and controlled studies.

This becomes particularly relevant at a time when experimental research itself is questioning long-held assumptions about the regenerative capacity of retinal ganglion cells.

Mouse studies cannot prove what occurs in the human optic nerve.

But neither can the absence of an established molecular explanation negate years of observations made directly in human patients.

The two approaches should meet.

Experimental research can identify mechanisms.

Long-term clinical observation can identify phenomena worth explaining.

The next step should therefore be prospective validation: standardized OCT endpoints, defined SLT protocols, carefully characterized normal-tension glaucoma populations, longitudinal RNFL and ganglion cell analysis, and appropriate control groups.

Only then can we determine whether the structural observations seen clinically represent pressure-mediated stabilization, altered rates of neurodegeneration, biological effects beyond IOP reduction — or potentially something we have not yet adequately defined.

Why a VISION PAPER™ Matters

This is also where the concept of the **VISION PAPER™** becomes relevant.

Scientific progress depends on evidence.

But evidence begins with a question.

Not every important observation originates within a university department, a large research consortium or an established academic programme.

Questions may emerge from decades of clinical practice, from repeated observations in patients, from unexpected findings or from connections between disciplines that have not previously been considered together.

Such observations should not be confused with proof.

But neither should they have to wait for institutional validation before they can be articulated as hypotheses.

Traditional scientific publishing performs an indispensable function. Peer review, methodological scrutiny, reproducibility and independent validation are essential when a hypothesis is to become scientific evidence.

Yet the pathway from an initial observation to a funded study, completed experiment, peer-reviewed manuscript and final publication can take years.

In rapidly developing fields, this creates an important gap between **what clinicians and scientists are beginning to observe and what the literature is already able to establish.**

The VISION PAPER™ is intended to occupy precisely this space.

It does not replace the scientific paper.

It precedes, connects and challenges it.

It provides a platform in which clinical observations, biological reasoning and emerging scientific evidence can be brought together transparently — with a clear distinction between **what is known, what has been observed and what is hypothesized.**

This distinction is fundamental.

A hypothesis does not become more valid because it originates from a prestigious institution.

Nor does a clinical observation become irrelevant because its mechanism has not yet been published.

Science advances when observations can be expressed, questioned, tested and, where necessary, rejected.

The purpose of a VISION PAPER™ is therefore not to bypass scientific standards.

It is to accelerate the generation of questions worthy of scientific testing.

This may be particularly important in medicine, where clinicians sometimes observe patterns in human patients years before the experimental tools, institutional structures or prospective studies required to explain them become available.

Editors, universities and peer-reviewed journals remain essential for validating evidence.

But the generation of ideas should remain open.

Scientific authority validates evidence.

It should not determine who is allowed to ask the question.

The faster meaningful observations can be transformed into testable hypotheses, the faster research can decide whether they are right or wrong.

And ultimately, that is what scientific progress requires.

A Broader Concept of Ocular Homeostasis

The eye is a biological system in continuous exchange.

Aqueous humor is produced, circulates through the anterior chamber and leaves primarily through the trabecular meshwork and Schlemm's canal.

The integrity of this pathway depends on living cells, extracellular matrix turnover, signalling molecules and immune surveillance.

Disturbance of such a system may therefore be more than a plumbing problem.

And restoring its function may be more than opening a drain.

This leads to a broader interpretation of SLT:

not simply as a laser that lowers pressure, but as an intervention capable of initiating a biological response within a dysfunctional outflow tissue.

Whether this response has consequences beyond aqueous outflow remains an open scientific question.

But it is precisely this question that deserves investigation.

Because if glaucoma — particularly normal-tension glaucoma — is increasingly understood as a disease involving cellular vulnerability, mitochondrial dysfunction, vascular regulation and impaired resilience, then treatment may ultimately need to operate on several biological levels simultaneously.

SLT may provide an instructive example of this transition.

We began using it because it lowers pressure.

We may eventually understand it more completely by asking **what it does to the tissue itself.**

And this leads directly to the next therapeutic question:

If cellular resilience determines whether a retinal ganglion cell survives, can we actively strengthen that resilience?

6.3 The Mitochondrion as a Therapeutic Target

If intraocular pressure does not fully explain why retinal ganglion cells degenerate, the next question must move deeper into the cell.

What determines whether a retinal ganglion cell can survive stress?

Increasingly, one answer points toward the mitochondrion.

Mitochondria are often described as the powerhouses of the cell.

For retinal ganglion cells, however, this description is almost too simple.

These neurons have exceptionally high energetic demands. They must maintain membrane potentials, generate action potentials, transport proteins and organelles along long axons, preserve synaptic function and continuously adapt to mechanical, vascular and metabolic stress.

All of this requires energy.

And much of that energy depends on mitochondrial function.

The question of glaucoma may therefore not only be how much stress reaches the retinal ganglion cell.

It may also be:

How much metabolic reserve does the cell have when that stress arrives?

Glaucoma as an Energetic Vulnerability

A retinal ganglion cell does not necessarily die because one single damaging event occurs.

Degeneration may result when multiple stresses converge on a cell whose capacity to compensate has progressively diminished.

Mechanical strain at the lamina cribrosa, impaired ocular perfusion, oxidative stress, disturbed axonal transport, neuroinflammation and ageing may all increase energetic demand while simultaneously reducing the cell's ability to meet it.

This creates a potentially dangerous mismatch:

energy demand rises while energy reserve falls.

Mitochondrial dysfunction is increasingly recognised as an important component of this vulnerability.

Altered oxidative phosphorylation, impaired mitochondrial dynamics, defective mitophagy and increased production of reactive oxygen species have all been implicated in retinal ganglion cell degeneration.

This may be particularly relevant in normal-tension glaucoma.

If pressure is not markedly elevated, another question becomes unavoidable:

Could some optic nerves fail not because the mechanical stress is extraordinarily high, but because their biological capacity to tolerate ordinary stress has become extraordinarily low?

This represents a fundamentally different therapeutic perspective.

ATP: The Energy Required to Survive

ATP is not simply cellular fuel.

It is required for maintaining ionic gradients, axonal transport, synaptic transmission, protein turnover and repair mechanisms.

The retinal ganglion cell and its long axon are particularly dependent on continuous energy availability.

When mitochondrial ATP production becomes insufficient, several processes may begin to fail simultaneously.

Axonal transport can become impaired.

Ion homeostasis becomes more difficult to maintain.

Oxidative damage accumulates.

Cellular repair mechanisms become less effective.

And eventually, pathways leading toward axonal degeneration and apoptosis may be activated.

This suggests that metabolic failure may not merely accompany neurodegeneration.

It may contribute to the transition from a stressed but viable neuron to an irreversibly damaged one.

NAD^+: More Than a Metabolic Molecule

One of the most interesting developments in glaucoma research concerns nicotinamide adenine dinucleotide — NAD^+.

NAD^+ is essential for cellular redox reactions and mitochondrial energy production.

But its biological significance extends considerably further.

It participates in cellular stress responses, DNA repair and signalling pathways involving sirtuins and other enzymes that regulate cellular survival and adaptation.

Experimental glaucoma research has demonstrated disturbances in NAD metabolism and has suggested that retinal ganglion cells may become increasingly vulnerable as NAD availability declines.

This has led to considerable interest in nicotinamide, a precursor of NAD^+, as a potential neuroprotective strategy.

Preclinical studies have produced striking results.

Nicotinamide supplementation has protected retinal ganglion cell somas, dendrites and axons in several experimental models and has been associated with improved mitochondrial function and resistance to metabolic stress.

Human evidence, however, remains preliminary.

Early phase clinical trials have shown encouraging physiological and functional signals, but current evidence is not sufficient to establish nicotinamide as a proven neuroprotective treatment for glaucoma.

This distinction is important.

Biological plausibility is not the same as clinical proof.

But biological plausibility tells us where to look.

Oxidative Stress: Cause, Consequence — or Both?

Mitochondrial dysfunction and oxidative stress are closely connected.

Mitochondria generate reactive oxygen species as a normal consequence of cellular respiration.

Under physiological conditions, antioxidant defence systems maintain these molecules within a controlled range.

When mitochondrial function deteriorates, however, reactive oxygen species may increase beyond the cell's capacity to neutralise them.

Proteins, lipids, mitochondrial membranes and DNA can then become damaged.

This creates the possibility of a self-amplifying cycle:

mitochondrial dysfunction → oxidative stress → mitochondrial damage → further energetic failure.

In glaucoma, oxidative stress has been described not only in the posterior segment and retinal ganglion cells but also within the trabecular meshwork.

This is an intriguing connection to the preceding discussion of SLT.

The anterior and posterior segments may not represent completely independent biological problems.

A dysfunctional outflow system and a vulnerable retinal ganglion cell may both reflect aspects of ageing, oxidative burden, impaired cellular clearance and declining biological resilience.

This does not mean that one necessarily causes the other.

But it suggests that glaucoma may need to be understood as more than a local pressure disorder.

Resveratrol and the Question of Cellular Resilience

This broader biological perspective has influenced our own therapeutic thinking for many years.

Alongside pressure management and SLT, we became increasingly interested in whether metabolic and mitochondrial support could help create a more favourable biological environment for retinal ganglion cell survival.

One molecule of particular interest has been **resveratrol**.

Resveratrol interacts with several pathways relevant to cellular stress responses, including SIRT1-related signalling, AMPK, oxidative stress regulation, inflammation and mitochondrial function.

Experimental glaucoma and retinal injury studies have reported protective effects on retinal ganglion cells, including reduced oxidative stress and apoptosis and improved cell survival.

More recent systematic analyses of preclinical studies have strengthened the biological rationale, reporting improved retinal ganglion cell survival and preservation of retinal structure across experimental models.

But here again, scientific precision is essential.

Most of this evidence remains **preclinical**.

It does not prove that oral resveratrol prevents glaucoma progression or regenerates retinal ganglion cells in humans.

Our clinical use and observations therefore represent a translational hypothesis rather than an established guideline-based neuroprotective treatment.

Yet the increasing convergence between mitochondrial biology, oxidative stress research, SIRT1-related pathways and retinal ganglion cell survival makes this hypothesis increasingly worthy of prospective investigation.

The relevant question is no longer simply whether resveratrol is an “antioxidant.”

That description may be too narrow.

The more interesting question is whether interventions influencing cellular energy regulation and stress-response pathways can alter the **resilience of the neuron itself**.

From Neuroprotection to Metabolic Neuroprotection

The term *neuroprotection* has been used in glaucoma for decades.

Yet many previous approaches focused on blocking a single downstream mechanism of neuronal injury.

The failure of some major neuroprotection trials should not necessarily be interpreted as evidence that neuroprotection itself is impossible.

It may indicate that the biological target, timing, endpoint or therapeutic strategy was incomplete.

A metabolically compromised neuron is unlikely to be rescued simply by blocking one final pathway of cell death.

Perhaps intervention must occur earlier.

Before irreversible structural loss.

Before energetic reserve is exhausted.

Before the axon reaches the point of no return.

This suggests a different concept:

Metabolic Neuroprotection

Instead of attempting only to inhibit neuronal death, metabolic neuroprotection would aim to maintain the biological capacity of the neuron to resist stress.

Potential targets include:

mitochondrial function,

NAD^+ availability,

ATP production,

oxidative stress regulation,

mitophagy,

axonal transport,

cellular stress-response pathways,

and vascular delivery of oxygen and metabolic substrates.

These mechanisms are interconnected.

And this may explain why a single intervention is unlikely to provide the complete answer.

Treating the Vulnerability, Not Only the Stressor

This brings us back to the central argument of this VISION PAPER™.

Pressure reduction reduces an important stressor.

SLT may additionally modify the biology of the outflow tissue.

But neither approach directly answers the question of why one retinal ganglion cell survives and another does not.

Mitochondrial biology introduces another therapeutic dimension:

the resilience of the target cell itself.

The emerging literature increasingly supports this shift. Mitochondrial dysfunction, NAD^+ depletion, oxidative stress and impaired metabolic adaptation are now being investigated not merely as consequences of glaucoma but as potential contributors to retinal ganglion cell vulnerability.

And early clinical research is beginning to move beyond animal models.

NAD^+-supporting interventions, metabolic therapies and other mitochondrial strategies are entering human studies. Preliminary clinical observations are appearing, although robust evidence of long-term structural neuroprotection remains absent.

This is exactly the stage at which scientific caution and scientific curiosity must coexist.

We should not present emerging metabolic interventions as proven glaucoma therapy.

But neither should we wait until retinal ganglion cells are irreversibly lost before asking whether their metabolic resilience could have been supported.

The therapeutic paradigm may therefore need to evolve:

Lower the pressure.

Restore ocular homeostasis.

Protect mitochondrial function.

Preserve cellular energy.

Strengthen neuronal resilience.

Not one instead of the other.

All as components of a more complete biological strategy.

Because ultimately, the objective of glaucoma treatment is not to achieve a particular number on a tonometer.

It is to keep the retinal ganglion cell alive.

6.4 From Neuroprotection to a Clinical Strategy

If mitochondrial dysfunction, impaired energy metabolism and reduced cellular resilience contribute to retinal ganglion cell vulnerability, the next question is unavoidable:

How can this knowledge be translated into clinical practice?

This is where caution becomes particularly important.

The biological rationale for neuroprotection in glaucoma is becoming increasingly compelling. Yet the evidence supporting individual neuroprotective interventions in humans remains substantially less developed than the evidence supporting intraocular pressure reduction.

The objective should therefore not be to replace established glaucoma therapy with experimental concepts.

It should be to ask whether established treatment can be embedded within a broader strategy designed to preserve the biological environment of the retinal ganglion cell.

Not One Treatment — but Several Levels of Protection

Glaucoma is unlikely to be successfully addressed by a single therapeutic mechanism.

If retinal ganglion cell degeneration results from the interaction of mechanical stress, vascular dysregulation, mitochondrial dysfunction, oxidative stress, impaired axonal transport, neuroinflammation and declining metabolic reserve, then treatment may ultimately need to operate on several levels simultaneously.

This suggests a layered therapeutic concept:

reduce mechanical stress,

improve ocular homeostasis,

identify vascular vulnerability,

support cellular energy metabolism,

reduce avoidable metabolic stress,

and monitor neuronal structure before irreversible function is lost.

The individual components are not equally established.

Some are already standard clinical practice.

Others are supported primarily by mechanistic or experimental evidence.

And some remain hypotheses requiring prospective validation.

The important point is not to confuse these levels of evidence.

It is to connect them.

Level 1: Reduce the Established Stressor

Intraocular pressure reduction remains the foundation of glaucoma treatment.

Medication, SLT and surgical procedures have established roles according to the individual patient's disease severity, target pressure and risk of progression.

Nothing in a metabolic or neuroprotective concept diminishes this.

On the contrary:

If the retinal ganglion cell is vulnerable, reducing unnecessary mechanical stress becomes even more important.

But normal-tension glaucoma demonstrates the limitation of stopping there.

When progression occurs despite apparently adequate pressure control, repeatedly lowering IOP without investigating the biological context may address only one component of the problem.

Level 2: Look for the Vulnerable Patient

A broader therapeutic strategy begins with a broader diagnostic strategy.

Not every patient with the same RNFL thickness, visual field defect or intraocular pressure has the same biological risk.

Particular attention may be warranted when structural progression appears disproportionate to pressure.

Potential contributors include impaired ocular perfusion, excessive nocturnal blood pressure reduction, vascular dysregulation, sleep-related abnormalities, metabolic dysfunction, nutritional deficiencies and other systemic factors capable of influencing neuronal energy supply or cellular stress.

This does not mean that every patient with glaucoma requires an indiscriminate battery of laboratory investigations.

It means that:

progression unexplained by pressure should trigger a search for what pressure does not explain.

The patient should not disappear behind the tonometry value.

Level 3: Protect Perfusion Without Simplifying It

Ocular perfusion represents one of the most compelling additional dimensions in normal-tension glaucoma.

The optic nerve requires continuous delivery of oxygen and metabolic substrates.

But perfusion is not simply equivalent to systemic blood pressure.

It depends on vascular autoregulation, endothelial function, local vascular resistance, nocturnal haemodynamics and the ability of the microcirculation to adapt to changing metabolic demand.

Both insufficient perfusion and unstable perfusion may matter.

This is particularly relevant at night.

A patient whose intraocular pressure appears excellent during daytime consultation may simultaneously experience substantial nocturnal systemic hypotension.

In such a situation, lowering pressure further may still be appropriate — but it may not address the complete physiological problem.

This argues for greater communication between ophthalmology and general medicine.

The optic nerve does not know which medical specialty is responsible for its blood supply.

Level 4: Support Metabolic Resilience — Without Pretending the Evidence Is Complete

The emerging field of metabolic neuroprotection introduces several potential therapeutic targets.

NAD^+ metabolism and nicotinamide are currently among the most actively investigated.

Coenzyme Q10 has attracted interest because of its role in mitochondrial electron transport and antioxidant defence.

Citicoline has been investigated for effects on neuronal membranes, neurotransmission and retinal ganglion cell function.

Resveratrol has attracted attention through pathways involving SIRT1, AMPK, mitochondrial function, oxidative stress and inflammatory regulation.

Other strategies targeting mitochondrial biogenesis, mitophagy, redox regulation and cellular energy metabolism are under investigation.

These approaches should not currently be presented as equivalent to established pressure-lowering therapy.

But neither should they all be dismissed under the imprecise label of “supplements.”

The relevant scientific question is not whether a substance belongs to a pharmaceutical or nutritional category.

It is:

Does it modify a biological pathway relevant to retinal ganglion cell survival, at an effective concentration, with acceptable safety — and can that effect ultimately be demonstrated in humans?

That question requires research.

Resveratrol: From Biological Rationale to Clinical Observation

Our own interest in resveratrol developed from precisely this perspective.

We have used resveratrol as part of a broader metabolic strategy in patients with glaucomatous neurodegeneration, particularly in combination with SLT and longitudinal OCT monitoring.

The rationale was not based simply on its frequently cited antioxidant properties.

Of greater interest were pathways associated with cellular stress adaptation and mitochondrial function, including SIRT1, AMPK and PGC-1α-related signalling.

These pathways are involved in mitochondrial biogenesis, energy regulation, oxidative stress responses and cellular survival.

Over years of clinical observation, this combination of pressure management, SLT and metabolic support has contributed to a working hypothesis:

Could improving the biological resilience of the retinal ganglion cell alter the trajectory of structural degeneration?

Again, observation is not proof.

Without randomized controls, changes in RNFL trajectory cannot automatically be attributed to resveratrol, SLT-induced biological effects or any single component of a multimodal strategy.

Regression to the mean, measurement variability, pressure reduction and the natural heterogeneity of glaucoma progression must all be considered.

But repeated observations can identify patterns.

And patterns can generate hypotheses worthy of formal investigation.

This is precisely where clinical medicine can contribute to the research process.

OCT-Guided Biological Intervention

These longitudinal observations have led us toward a concept that we propose to describe as **OCT-Guided Biological Intervention**.

Rather than allowing intraocular pressure alone to determine when treatment should be initiated or repeated, longitudinal OCT becomes an active component of therapeutic decision-making.

The individual trajectory of RNFL and ganglion cell structures is followed over time.

When renewed structural decline becomes reproducible, the question is not only whether pressure should be lowered further, but whether the biological environment of the eye should be therapeutically addressed again.

In our clinical approach, this has included repeat SLT combined with resveratrol-based metabolic support, followed by renewed structural monitoring.

OCT therefore changes its role: from a diagnostic instrument documenting damage to a longitudinal biological feedback tool guiding intervention.

This concept does not imply that every fluctuation in RNFL thickness should trigger treatment.

Reproducibility, segmentation quality, measurement variability and the complete clinical picture remain essential.

But when a consistent structural trajectory changes, OCT may provide information that precedes clinically apparent functional loss.

OCT-Guided Biological Intervention therefore proposes a dynamic therapeutic model: observe the neuron, identify renewed structural vulnerability, intervene when appropriate, and measure the biological response longitudinally.

This concept requires prospective validation.

But it offers a framework for moving glaucoma management from fixed treatment algorithms toward an individualized response to the behaviour of the patient's own neuronal tissue.

Repeated Intervention — and a Repeated Structural Observation

An additional observation became particularly relevant during longitudinal follow-up.

In some patients, an initial increase or stabilization of RNFL thickness following SLT and metabolic support was not necessarily permanent.

When subsequent OCT examinations again demonstrated a decline in RNFL thickness, we did not automatically interpret this as the end of therapeutic opportunity.

Instead, SLT was repeated, accompanied by resveratrol-based metabolic support.

In a number of these longitudinally observed eyes, we subsequently observed **another increase in measured RNFL thickness**.

The significance of this observation should be interpreted carefully.

An increase in OCT-measured RNFL thickness cannot, by itself, be equated with regeneration of retinal ganglion cells. Measurement variability, segmentation effects, changes in tissue characteristics and other confounding factors must be considered.

Nevertheless, the observation becomes more difficult to dismiss when a similar structural pattern appears repeatedly in temporal association with repeated intervention.

This creates an important hypothesis:

If structural decline can be followed by stabilization or an increase in measured RNFL thickness after an intervention — and if a similar response can be observed again after renewed decline and repeated treatment — are we observing only measurement variability, or are we influencing a modifiable biological process?

The question becomes particularly relevant because SLT itself is a repeatable intervention.

When performed appropriately and with controlled energy, repeat SLT can be used when its effect diminishes or when further treatment becomes necessary.

This creates the possibility of thinking about SLT not necessarily as a single lifetime event, but as an intervention that may be reconsidered according to longitudinal structural and clinical findings.

Our clinical approach has therefore increasingly been guided not only by a fixed treatment schedule, but by **longitudinal OCT behaviour**.

When RNFL measurements suggested renewed structural decline, this became a reason to reassess the biological and therapeutic situation rather than simply wait for further loss.

The combination of repeated SLT, metabolic support and subsequent structural observation does not establish causality.

But the apparent reproducibility of the pattern makes it scientifically relevant.

A single unexpected observation may be incidental.

A repeatedly observed response following repeated intervention becomes a hypothesis that deserves to be tested.

The longitudinal pattern can therefore be conceptualized as:

Structural decline → biological intervention → OCT response → longitudinal observation → renewed decline → repeated intervention → renewed OCT response.

Future prospective studies should examine not only whether SLT lowers intraocular pressure after initial and repeated treatment, but whether repeated intervention is associated with reproducible changes in the **rate and direction of longitudinal RNFL and ganglion cell trajectories**.

This could help distinguish measurement variability and pressure-mediated stabilization from a potentially broader biological response.

Until such studies are performed, the interpretation must remain cautious.

But the observation itself should not be ignored.

The Endpoint Must Change

If future glaucoma research is to test metabolic neuroprotection, the choice of endpoints becomes critical.

Waiting for advanced visual field deterioration may be too late to understand early biological effects.

Modern OCT allows us to observe structural change longitudinally.

RNFL thickness, macular ganglion cell parameters and rates of structural progression can therefore become important components of prospective neuroprotection studies.

But even OCT requires careful interpretation.

Stabilization is not regeneration.

Measurement variability is not neuronal recovery.

And an apparent increase in RNFL thickness should never automatically be interpreted as restoration of retinal ganglion cells.

If regeneration is proposed, the evidentiary threshold must be substantially higher.

Structural findings would need to be reproducible, longitudinal and ideally accompanied by functional and biological correlates.

This distinction is essential because the possibility of neuronal restoration is now being actively reconsidered experimentally.

Research demonstrating axonal regeneration and restoration of visual function in animal models has challenged the traditional assumption that adult retinal ganglion cell damage is invariably irreversible.

That does not establish regeneration in human glaucoma.

But it changes the scientific question from:

“Is regeneration impossible?”

to:

“Under what biological conditions might restoration become possible?”

Prevention May Begin Before Neuroprotection

There is another consequence of this thinking.

Perhaps the most effective neuroprotection occurs before a neuron requires rescue.

If mitochondrial reserve declines gradually with ageing, metabolic disease, oxidative burden, vascular dysfunction and chronic cellular stress, then maintaining systemic health may indirectly influence neuronal resilience long before glaucoma becomes clinically advanced.

This brings ophthalmology into a much broader medical context.

Sleep.

Movement.

Metabolic health.

Blood pressure regulation.

Nutritional adequacy.

Avoidance of smoking.

Management of diabetes and vascular risk.

Circadian stability.

These should not be presented as proven treatments capable of stopping glaucoma.

But they influence biological systems upon which neuronal survival depends.

The distinction is subtle but important.

A healthy lifestyle is not a substitute for glaucoma treatment.

It may, however, contribute to the biological environment in which glaucoma treatment must succeed.

From Standard Therapy to Precision Neuroprotection

The future may therefore not lie in finding one universal “neuroprotective drug.”

It may lie in identifying different forms of vulnerability.

One patient may predominantly require aggressive pressure reduction.

Another may have pronounced vascular dysregulation.

Another may demonstrate metabolic vulnerability.

Another may combine several of these factors.

This suggests a transition from a uniform pressure-centred model toward **precision neuroprotection**.

Not every patient needs every intervention.

But every patient deserves the question:

What is driving progression in this particular eye?

Such an approach would combine established ophthalmological treatment with increasingly precise structural monitoring and, where indicated, investigation of systemic and metabolic contributors.

The purpose is not to medicalise every aspect of life.

It is to recognise that the retinal ganglion cell is part of a living human organism.

A Proposed Therapeutic Framework

The therapeutic strategy emerging from this VISION PAPER™ can therefore be summarised in five steps:

1. Detect neuronal damage early.

Do not wait for elevated pressure to initiate the search for glaucoma.

2. Reduce modifiable mechanical stress.

Lower intraocular pressure according to established evidence and individual risk.

3. Restore and maintain ocular homeostasis.

Consider the biological effects of interventions such as SLT in addition to their measurable pressure response.

4. Identify systemic and metabolic vulnerability.

When progression is not adequately explained by pressure, investigate factors capable of compromising perfusion, energy metabolism and neuronal resilience.

5. Explore neuroprotective strategies while maintaining scientific discipline.

Use emerging biological knowledge to generate and test interventions — while clearly distinguishing established therapy from translational hypotheses.

This is not a rejection of conventional glaucoma treatment.

It is its extension.

For decades, ophthalmology has become increasingly sophisticated in lowering intraocular pressure.

The next stage may require the same sophistication in understanding the patient whose optic nerve continues to deteriorate despite it.

Toward a Dynamic Treatment Model

The future of glaucoma therapy may therefore require a **dynamic rather than a static treatment model**:

Detect structural change early.

Intervene before irreversible loss.

Follow the neuronal response.

And intervene again when renewed vulnerability becomes visible.

This is the principle we propose as:

OCT-Guided Biological Intervention

6.5 Perfusion, Metabolism and the Whole Patient

Glaucoma occurs in the eye.

But the retinal ganglion cell lives within the biology of the whole patient.

This distinction becomes particularly important in normal-tension glaucoma.

When intraocular pressure is not markedly elevated, factors outside the traditional pressure model deserve greater attention. Ocular perfusion, vascular autoregulation, systemic blood pressure, metabolic health, sleep and cellular energy availability may all influence the environment in which the optic nerve must survive.

The Optic Nerve Depends on More Than Pressure

Adequate neuronal function requires a continuous supply of oxygen and metabolic substrates.

This supply depends not simply on blood pressure, but on the ability of the microcirculation to adapt to changing demand.

A patient may have apparently normal cardiovascular measurements during the day while experiencing substantial nocturnal blood pressure reductions, disturbed vascular regulation or periods of reduced ocular perfusion.

Particularly in normal-tension glaucoma, such patterns may matter.

The therapeutic question should therefore not always be:

How much lower can we make the intraocular pressure?

It may also be:

Is the optic nerve receiving what it needs to maintain cellular function?

Metabolism Connects the Eye to the Body

Mitochondrial function does not exist independently of systemic metabolism.

Glucose regulation, insulin sensitivity, micronutrient availability, vascular health, inflammatory signalling, oxidative burden and homocysteine metabolism are among the systemic factors capable of interacting with cellular energy production and vascular function.

Their precise contribution to glaucoma progression differs in strength of evidence and should not be overstated.

But the biological principle is difficult to ignore:

The retina cannot be metabolically separated from the organism that supplies it.

This has consequences for clinical thinking.

When structural deterioration continues despite apparently adequate pressure management, looking beyond the eye should not be regarded as abandoning ophthalmology.

It may represent a more complete form of ophthalmology.

Sleep, Circadian Biology and Recovery

Sleep deserves particular attention.

It influences autonomic regulation, blood pressure patterns, glucose metabolism, mitochondrial function, inflammatory signalling and cellular repair.

At the same time, nighttime physiology creates a unique situation for the optic nerve: systemic blood pressure may fall while intraocular pressure can change in the opposite direction.

This interaction may be especially relevant in vulnerable individuals.

Again, this does not make sleep therapy a treatment for glaucoma.

But it illustrates why the biological environment of the optic nerve cannot be understood from a daytime IOP measurement alone.

From the Eye to the Individual

A more integrated approach therefore does not require abandoning established glaucoma algorithms.

It requires adding another layer of questions.

What is the patient's vascular situation?

What happens at night?

Is there evidence of metabolic vulnerability?

Are potentially modifiable systemic factors present?

And does the longitudinal OCT trajectory change when these factors and ocular treatment are addressed together?

The purpose is not to transform glaucoma into a vaguely defined systemic disease.

It is to recognise that **neuronal survival is a systemic biological achievement.**

The eye may reveal the damage.

But the conditions determining resilience may extend far beyond it.

And this leads to a final perspective.

If modern molecular medicine increasingly describes health in terms of **homeostasis, resilience, adaptation and the capacity to recover from stress**, it is worth asking whether these concepts are entirely new.

Or whether other medical traditions have been describing aspects of the same fundamental biological principle in a different language for centuries.

This is where Ayurveda offers an interesting perspective — not as a substitute for molecular science, but as another way of thinking about regulation, individual vulnerability and the preservation of balance.

6.6 A Different Language for Resilience: What Ayurveda May Add to the Question

Modern glaucoma research is increasingly moving toward concepts such as cellular resilience, metabolic reserve, mitochondrial function, vascular regulation and the capacity of neurons to adapt to stress.

These concepts belong to modern molecular medicine.

Yet the underlying idea — that health depends not only on the absence of a damaging factor, but on the organism's ability to maintain and restore balance — is much older.

Ayurveda offers an interesting perspective in this context.

Not because Ayurvedic concepts can be equated with mitochondrial biology, retinal ganglion cell metabolism or modern neurophysiology.

They cannot.

And not because traditional medicine should replace evidence-based glaucoma treatment.

It should not.

The value lies elsewhere.

A Different Way of Describing Vulnerability

Ayurvedic medicine views health as a dynamic state of regulation rather than simply the absence of disease.

Individual constitution, environmental influences, nutrition, sleep, stress, ageing and daily rhythms are considered part of a continuously changing biological balance.

Disease is therefore not understood exclusively as an isolated defect in one organ.

It may emerge when the organism progressively loses its ability to compensate for internal and external disturbance.

The terminology is different from that of molecular medicine.

But the question is surprisingly familiar:

Why does one individual remain stable under a particular stress while another becomes vulnerable?

Modern glaucoma research asks essentially the same question when two patients with similar intraocular pressure develop completely different trajectories of retinal ganglion cell loss.

Vata, Pitta and Kapha Are Not Molecular Pathways

Scientific discipline requires a clear boundary.

The Ayurvedic concepts of Vata, Pitta and Kapha should not be translated directly into neurotransmitters, mitochondrial pathways, inflammatory mediators or vascular mechanisms.

Such one-to-one comparisons would oversimplify both systems.

They are different explanatory frameworks developed in different historical and scientific contexts.

But Ayurveda contributes something that modern highly specialised medicine can sometimes lose:

attention to patterns.

Sleep and wakefulness.

Activity and recovery.

Nutrition and digestion.

Stress and adaptation.

Environment and season.

Individual constitution and individual response.

Rather than asking only which isolated parameter is abnormal, Ayurveda traditionally asks whether the organism as a whole remains capable of maintaining equilibrium.

This does not provide a molecular explanation for glaucoma.

But it may encourage a clinically valuable question:

What is reducing this patient's capacity to compensate?

From Balance to Homeostasis

Modern physiology uses a different vocabulary.

We speak of homeostasis.

Allostasis.

Autonomic regulation.

Circadian biology.

Mitochondrial reserve.

Metabolic flexibility.

Oxidative balance.

Vascular autoregulation.

Cellular stress responses.

These concepts are measurable and increasingly mechanistically defined.

Yet they share a broad principle:

Biological systems survive by continuously adapting to change.

A healthy system is not static.

It is capable of being disturbed and returning toward equilibrium.

This may also be relevant to the retinal ganglion cell.

The therapeutic goal may therefore not simply be to remove every possible stressor.

That is impossible.

It may be to reduce excessive stress while preserving or strengthening the biological capacity to respond to it.

East and West Should Not Compete

The future of medicine does not require choosing between traditional and modern thinking.

It requires knowing what each can — and cannot — contribute.

Modern science provides measurement, mechanism, controlled experimentation and the ability to test causality.

Traditional medical systems may contribute long-developed observations about individual variability, rhythms, behaviour, environment and the relationship between different aspects of health.

One should not be used to validate the other without evidence.

But different perspectives can generate new questions.

And new questions are precisely where scientific discovery begins.

Perhaps the most productive relationship between Eastern and Western medicine is therefore not one of equivalence.

It is one of **intellectual dialogue**.

A traditional concept may inspire a hypothesis.

Modern science must then determine whether that hypothesis survives measurement and experimentation.

This principle is entirely consistent with the purpose of the VISION PAPER™:

to connect observations and disciplines without confusing hypothesis with proof.

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Conclusion — From Lowering Pressure to Preserving the Neuron

Glaucoma treatment has achieved something remarkable.

We can measure intraocular pressure precisely.

We can lower it pharmacologically, with laser treatment and surgically.

And doing so protects vision.

None of this should be diminished.

But normal-tension glaucoma confronts us with an uncomfortable fact:

Retinal ganglion cells can degenerate even when intraocular pressure was never conventionally elevated.

This means that pressure is critically important — but it cannot be the entire biological explanation.

VISION PAPER™ No. 6 therefore proposes an expanded therapeutic perspective.

The first principle remains established:

reduce modifiable mechanical stress.

But beyond pressure, we should investigate the biological conditions that determine neuronal vulnerability.

SLT provides an intriguing example.

What began as a pressure-lowering laser procedure is increasingly understood to initiate biological processes involving monocytes and macrophages, cytokine signalling, extracellular matrix remodelling and trabecular cellular behaviour.

Our long-term clinical observations raise the further hypothesis that its therapeutic relevance may not always be fully represented by the magnitude of pressure reduction alone.

The same expansion of thinking applies to the retinal ganglion cell itself.

Mitochondrial function, NAD^+ metabolism, ATP availability, oxidative stress, vascular supply and cellular stress responses are increasingly becoming part of the scientific discussion surrounding glaucoma neurodegeneration.

This leads from pressure reduction toward **metabolic neuroprotection**.

And clinical observation adds another dimension.

In longitudinal OCT follow-up, we have observed structural trajectories in which RNFL decline was followed by stabilization or an increase in measured RNFL thickness after SLT combined with resveratrol-based metabolic support. In some patients, renewed structural decline was followed by repeated intervention and subsequently by another measured increase.

These observations do not prove retinal ganglion cell regeneration.

They do not establish causality.

But their repetition creates a hypothesis that should be tested rather than ignored.

From these observations we propose the concept of:

OCT-Guided Biological Intervention

A dynamic model in which OCT is not used merely to document damage after it has occurred, but to follow neuronal structure longitudinally, identify renewed vulnerability, guide reassessment and intervention, and subsequently observe the structural response.

The sequence becomes:

Detect → Intervene → Observe → Reassess → Intervene Again When Necessary.

This is not yet an established therapeutic algorithm.

It is a proposal for investigation.

And that distinction represents the central philosophy of the VISION PAPER™ itself.

Science requires evidence.

But before evidence exists, someone must be permitted to observe.

Someone must connect findings that have previously remained separate.

And someone must formulate the question.

Clinical observations in humans should not be considered irrelevant simply because experimental mechanisms are still being investigated in animals or because prospective trials have not yet been completed.

Nor should experimental findings be translated prematurely into clinical claims.

The two must meet.

The future of glaucoma therapy may therefore not be defined by one new drug, one new laser or one new biomarker.

It may emerge from a change in perspective:

from pressure to vulnerability,

from damage to resilience,

from static diagnosis to longitudinal biological observation,

and from treating an isolated eye to understanding the biology of the individual in whom that eye exists.

Eastern and Western medicine may describe aspects of resilience in very different languages.

Modern science must determine which mechanisms are real, measurable and therapeutically relevant.

But both perspectives remind us of something fundamental:

Survival is not simply the absence of stress.

It is the capacity to respond to it.

And perhaps that is the deeper therapeutic question in glaucoma:

Not only how do we lower the pressure — but how do we help the neuron survive?
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