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Small-Molecule Therapeutics for Retinal Neurodegenerative Diseases: Towards Enhanced Neuroprotection

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Abstract

Retinal neurodegenerative diseases, including glaucoma and age-related macular degeneration (AMD), are among the leading causes of irreversible vision loss worldwide. Current therapeutic options remain limited, in part because many biologics and other macromolecular agents exhibit inadequate penetration across the blood–retinal barrier and often require invasive administration routes, which can compromise adherence. Small-molecule drugs have emerged as promising candidates for retinal neuroprotection and disease modification due to their favorable physicochemical tunability, lower manufacturing costs, potential for noninvasive delivery, and improved tissue penetration. This paper outlines recent advances in small-molecule development for retinal neurodegeneration with an emphasis on mechanism-driven classification. We summarize representative strategies targeting oxidative stress, inflammatory and immune signaling, and neuroprotective pathways associated with mitochondrial dysfunction and apoptosis. Particular attention is given to the multi-target potential of single small molecules, reflecting the multifactorial nature of retinal degeneration where oxidative injury and chronic inflammation frequently coexist. Finally, we discuss key translational barriers such as short intraocular half-life, off-target effects, and dosing limitations, and

highlight future directions that integrate nanotechnology-based delivery systems to enhance ocular bioavailability, sustain drug release, and improve safety profiles. Together, this framework aims to support mechanism-informed drug design and accelerate the clinical translation of small-molecule therapies for retinal neurodegenerative disorders.

Keywords: Retinal neurodegeneration; glaucoma; age-related macular degeneration; small-molecule drugs; oxidative stress; nanocarriers

1. Introduction

1.1 Clinical and Societal Burden

Retinal neurodegenerative diseases, including glaucoma and age-related macular degeneration (AMD), represent leading causes of irreversible vision loss worldwide. It is estimated that over 80 million people suffer from glaucoma (Adhikari et al., 2021), and this number is expected to rise to over 111.8 million by 2040 (Omorova et al., 2024). In AMD, the global prevalence is estimated at approximately 196 million, with a projected increase to 288 million by 2040 (Romond et al., 2021). These diseases lead to not only significant medical costs but also a profound impact on patients' quality of life, including decreased independence, higher risk of falls and injuries, and social isolation. Vision impairment also correlates with increased rates of depression and cognitive decline, particularly in older adults (Sano et al., 2019).

The public health implications of retinal neurodegeneration are substantial. Vision loss is not only a medical outcome but also a societal determinant of quality of life, independence, and economic productivity. Progressive visual impairment increases risks of falls and injuries, limits mobility and social participation, and is frequently associated with depression and cognitive burden in older adults. Importantly, the irreversibility of neuronal loss in the retina means that delayed intervention often translates into permanent disability; once retinal ganglion cells (RGCs) or photoreceptors are lost, current clinical approaches have limited capacity to restore function (Chen et al., 2025). Despite advances in diagnostics and symptomatic treatments, a significant unmet clinical need persists for therapies that can preserve neuronal

integrity, slow disease progression, and meaningfully extend the window of functional vision.

1.2 Limitations of Current Therapies

Current therapeutic paradigms for major retinal neurodegenerative diseases frequently emphasize risk-factor control or late-stage complication management rather than direct neuroprotection or disease modification. In glaucoma, for example, intraocular pressure (IOP) lowering remains the cornerstone of treatment and is effective in many patients (Makhijani et al., 2026); however, a clinically important subset continues to progress despite adequate IOP control, suggesting that additional mechanisms—such as mitochondrial dysfunction, vascular dysregulation, and neuroinflammation—contribute to ongoing RGC loss (Liu et al., 2025). Similarly, in AMD, especially neovascular AMD, anti-VEGF therapy has transformed outcomes for many patients by stabilizing or improving vision in the short to medium term. Yet these treatments do not fully address the underlying degenerative processes, and outcomes can remain suboptimal due to incomplete response, disease heterogeneity, and persistent structural decline (Yang et al., 2025).

A major obstacle to effective retinal neurotherapeutics lies in drug delivery. The eye is protected by layered anatomical and physiological barriers that safeguard neural tissue yet impede pharmacological access. The blood–retinal barrier (BRB) restricts systemic drug penetration into the retina (Liu et al., 2025), while corneal and conjunctival barriers limit posterior segment delivery from topical administration (Shahror et al., 2025). As a result, many agents—particularly large molecules and biologics—require intravitreal injection to achieve therapeutic concentrations in the posterior segment. Although intravitreal delivery is clinically feasible, it introduces practical and clinical drawbacks: repeated injections increase treatment burden, elevate cumulative risk of complications (e.g., infection, hemorrhage, retinal detachment), and can reduce long-term adherence (Phan et al., 2025).

Adherence itself is a nontrivial constraint across retinal diseases. Chronic disorders require sustained therapy, yet frequent clinic visits, complex dosing schedules, and patient discomfort can erode persistence over time. Even when effective drugs exist, real-world outcomes may

underperform clinical trial results due to adherence gaps. Collectively, these limitations underscore a critical gap between symptom control and the goal of true neuroprotection—namely, therapies that directly preserve retinal neurons, maintain synaptic and mitochondrial function, and meaningfully alter the natural course of degeneration (Makhijani et al., 2026) .

1.3 Rationale for Small-Molecule Approaches

Against this backdrop, small-molecule drugs have gained increasing attention as candidates for retinal neurodegenerative diseases. From a drug-development perspective, small molecules offer several advantages that align with the key constraints in ocular therapeutics. First, their physicochemical tunability enables rational optimization of permeability, solubility, stability, and receptor selectivity—properties essential for crossing ocular barriers and reaching the retina at effective concentrations. Second, compared with biologics, small molecules often allow more flexible delivery strategies, including oral or topical administration in selected contexts, which may improve patient acceptance and adherence when posterior segment exposure can be achieved or when formulation technologies are leveraged (Shahror et al., 2025). Third, small molecules support structure–activity relationship (SAR)-driven iterative improvement and can be designed to target intracellular pathways that are difficult to modulate with large molecules. This is particularly relevant for retinal neurodegeneration, where key processes—oxidative stress responses, mitochondrial quality control, apoptosis signaling, and inflammatory transcriptional programs—operate within cells and organelles. Fourth, small molecules generally enable scalable and cost-efficient manufacturing, which can be important for broad population-level implementation, especially in long-term chronic therapy.

Crucially, retinal neurodegeneration is multifactorial; oxidative stress, inflammation, metabolic dysregulation, and mitochondrial failure often interact interdependently. Small molecules may therefore be especially suited to combination therapy or multi-target pharmacology, either through drug cocktails or via single agents capable of modulating multiple interconnected pathways. Such strategies align with a disease model in which modest, coordinated effects across several nodes of the degenerative network may outperform highly selective modulation

of a single pathway (Martucci et al., 2025).

1.4 Organization of the Paper

The remainder of this paper is structured to move from biological rationale to translational strategy in a stepwise manner. First, we summarize the shared pathophysiological processes that create actionable targets for pharmacological intervention in retinal neurodegeneration. Next, we review small-molecule therapies classified by primary mechanism, focusing on antioxidant/redox-modulating agents, anti-inflammatory or immunomodulatory agents, and neuroprotective molecules targeting mitochondrial dysfunction and apoptotic pathways. Building on this foundation, we then examine the rationale and evidence for multi-target strategies, including whether single small molecules can plausibly address multiple disease-driving mechanisms such as oxidative stress and inflammation concurrently. Finally, we discuss the key bottlenecks that currently limit clinical translation—including pharmacokinetic constraints, safety concerns, and delivery challenges—and conclude with a focused outlook on how nanotechnology-based delivery systems may overcome these barriers by enhancing retinal exposure, prolonging intraocular residence time, and improving overall therapeutic indices.

2. Pathophysiological Basis for Small-Molecule Intervention

2.1 Shared Degenerative Mechanisms Across Glaucoma and AMD

Although glaucoma and AMD differ in their initiating factors and primary anatomical sites of injury, both converge on a limited set of biological processes that drive progressive neuronal dysfunction and loss. This convergence is clinically important because it implies that therapeutics targeting fundamental stress-response pathways may have relevance across multiple retinal neurodegenerative phenotypes (Grosso et al., 2025).

Oxidative stress and redox imbalance represent a central pathogenic axis. The retina is metabolically demanding and continuously exposed to light, making it intrinsically susceptible to reactive oxygen species (ROS) generation. In glaucoma, oxidative stress contributes to RGC vulnerability and axonal degeneration (Maddineni et al., 2025), while in AMD, chronic oxidative injury is closely linked to RPE dysfunction, photoreceptor loss, and downstream inflammatory activation (Mimura et al., 2025). Persistent redox disequilibrium can damage lipids, proteins, and nucleic acids, destabilize cellular membranes, and amplify degenerative signaling through self-reinforcing feedback loops (Makhijani et al., 2026).

Closely coupled to oxidative injury is mitochondrial dysfunction, which is increasingly viewed as a final common pathway in retinal neurodegeneration. Mitochondria govern ATP production, calcium buffering, and apoptosis regulation—functions critical for long-lived neurons such as RGCs and photoreceptors. When mitochondrial dynamics (fusion/fission balance), quality control, or membrane potential are disrupted, retinal neurons may enter a state of bioenergetic failure characterized by reduced ATP availability, increased ROS production, and impaired axonal transport. This vulnerability is particularly pronounced in RGCs because of their long axons and high energy requirements (Maddineni et al., 2025).

Neuroinflammation and immune dysregulation further shape disease progression. In both glaucoma and AMD, microglia and other innate immune components can transition from protective surveillance to chronic activation, releasing cytokines, chemokines, and reactive intermediates that exacerbate neuronal stress (J. Li et al., 2025; Wu et al., 2026). In AMD, inflammation is often discussed in the context of complement activation and chronic para-inflammatory states, whereas in glaucoma, neuroinflammatory signaling within the optic nerve head and inner retina is commonly implicated in accelerating RGC loss. Importantly, inflammation and oxidative stress frequently co-amplify: oxidative injury promotes inflammatory signaling, and inflammation in turn increases oxidative burden (Akaiwa et al., 2017).

Downstream of these processes, retinal cells activate apoptosis and regulated cell death pathways, which translate chronic stress into irreversible cellular loss. Mitochondria-mediated apoptosis—through cytochrome c release and caspase activation—has been widely studied in RGC and photoreceptor degeneration. In parallel, dysregulated calcium homeostasis, excitotoxic signaling, and impaired neurotrophic support can act as upstream triggers that push stressed neurons toward death programs (Maddineni et al., 2025; Sun et al., 2025).

Beyond these core mechanisms, several additional contributors deserve mention because they influence therapeutic target selection and delivery strategy. Vascular and metabolic dysregulation can reduce oxygen and nutrient supply to retinal tissues, intensifying oxidative stress and mitochondrial failure. Proteostasis imbalance—including impaired autophagy and accumulation of damaged proteins/organelles—can further compromise neuronal survival. Collectively, these interconnected processes create a disease network in which multiple pathways operate simultaneously rather than sequentially, helping explain why single-mechanism interventions may show limited durability in complex clinical settings (Sano et al., 2019). The shared pathogenic pathways and potential intervention points are illustrated in Figure 1.

2.2 Therapeutic Implications for Small-Molecule Development

The mechanistic landscape described above has several direct implications for the design and translation of small-molecule therapies.

First, because retinal neurodegeneration is driven by interdependent pathways, an effective therapeutic strategy often requires either (i) targeting a nodal regulator that influences several downstream cascades, or (ii) adopting a multi-target approach that modulates oxidative stress, inflammation, and mitochondrial stability in a coordinated manner. This is one reason small molecules are attractive: they can be engineered to act intracellularly, reach organelle-associated targets, and—depending on chemistry and formulation, exhibit pharmacology that

spans multiple mechanistic domains (Martucci et al., 2025).

Second, translational success depends not only on mechanistic plausibility but also on establishing a credible pharmacokinetic/pharmacodynamic (PK/PD) bridge to the retina. For small molecules, this typically means demonstrating that the candidate reaches relevant retinal compartments at concentrations sufficient to engage its target(s) and produce measurable biological effects. In retinal neurodegeneration, target engagement may be inferred using biomarkers linked to oxidative stress reduction, inflammatory signaling attenuation, mitochondrial function restoration, or apoptosis suppression, alongside functional readouts such as electrophysiology and visual behavior in animal models (Zhang et al., 2025).

Third, the degenerative course is slow and heterogeneous, which underscores the importance of endpoint selection. A recurring limitation in neuroprotective development is relying on short-term surrogate outcomes that do not translate into sustained functional preservation. Therefore, candidates should ideally show converging evidence across (i) structural preservation (e.g., retinal layer integrity), (ii) cellular survival (e.g., RGC/photoreceptor counts), and (iii) functional outcomes (e.g., electrophysiological responses), with appropriate attention to dosing duration and safety.

Finally, these mechanisms emphasize that efficacy is inseparable from delivery feasibility. Even highly potent small molecules may fail clinically if they cannot be maintained in the posterior segment at therapeutic levels without unacceptable toxicity or patient burden. This reality motivates the later focus of this review: integrating small-molecule pharmacology with nanotechnology-enabled delivery systems to enhance retinal exposure, prolong intraocular residence time, reduce dosing frequency, and improve therapeutic index.

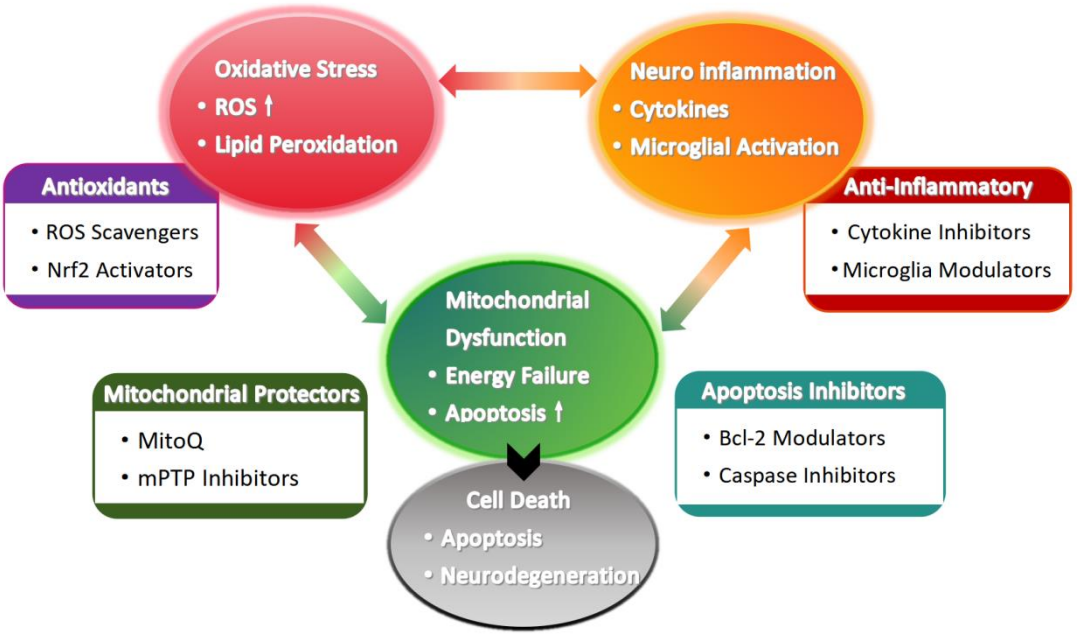

Figure 1. Shared pathogenic pathways (oxidative stress–inflammation–mitochondria–apoptosis) and intervention points of small molecules

3. Small-Molecule Therapeutics Classified by Mechanism of Action

Given the multifactorial nature of retinal neurodegenerative diseases, mechanism-based classification provides a practical framework for evaluating small-molecule candidates. In this section, small molecules are grouped according to their dominant therapeutic intent—redox control, inflammation/immune modulation, and direct neuroprotection (with emphasis on mitochondrial stability and apoptotic pathways). While these categories are conceptually distinct, they are biologically intertwined; in many cases, a compound initially developed for a single pathway may exert secondary benefits through pathway crosstalk. Accordingly, the goal of this section is not to rigidly compartmentalize agents but to clarify the mechanistic logic that motivates their development and the types of evidence typically used to support translational relevance.

3.1 Antioxidant and Redox-Modulating Small Molecules

Oxidative stress is a recurring driver of retinal injury across glaucoma and AMD, making redox modulation one of the most consistently pursued small-molecule strategies. Conceptually, antioxidant therapies can be divided into two broad approaches: direct neutralization of reactive species and indirect reinforcement of endogenous antioxidant defenses (Maddineni et al., 2025).

Direct antioxidants aim to reduce oxidative burden by scavenging reactive oxygen species (ROS) or limiting radical propagation in lipid-rich retinal membranes. This approach is intuitively appealing given the retina's high oxygen consumption and susceptibility to photo-oxidative injury. However, direct scavenging alone can be limited by pharmacokinetic constraints and the difficulty of sustaining therapeutic concentrations in relevant retinal compartments. Moreover, oxidative stress is often a downstream readout of broader metabolic and inflammatory dysregulation; therefore, direct antioxidant activity may be insufficient unless upstream drivers are also addressed (Mimura et al., 2025).

In response to these limitations, increasing attention has shifted toward indirect redox modulation, in which small molecules activate or stabilize the cell's intrinsic defense systems. A common mechanistic theme is the enhancement of transcriptional programs that govern detoxification enzymes, glutathione homeostasis, and oxidative damage repair. Such "endogenous defense boosting" approaches are attractive because they can produce broader, longer-lasting protective effects than short-lived ROS scavenging, potentially improving durability in chronic neurodegeneration (Morette et al., 2026).

A particularly relevant sub-strategy is mitochondria-centered redox control. Because mitochondrial dysfunction both produces ROS and amplifies energy failure, compounds that improve mitochondrial resilience can create a twofold benefit: reducing oxidative byproducts while restoring cellular bioenergetics. In retinal neurons, which are highly energy-dependent, preserving mitochondrial function can be especially important for maintaining axonal transport, synaptic activity, and survival signaling (Sun et al., 2025).

Representative candidates and evidence:

Edaravone, a potent antioxidant, has been evaluated in clinical trials for glaucoma and has

shown a reduction in oxidative stress and preservation of retinal function in animal models (Akaiwa et al., 2017).

N-Acetylcysteine (NAC), which enhances glutathione levels and scavenges ROS, has demonstrated neuroprotective effects in animal models of both glaucoma and retinal ischemia (Sano et al., 2019).

MitoQ, a mitochondria-targeted antioxidant, improves mitochondrial function and reduces oxidative damage, particularly in retinal ganglion cells (RGCs) in preclinical models (Kim et al., 2024) .

However, while these agents show promise in animal studies, challenges remain in achieving adequate retinal penetration and sustained therapeutic levels in the posterior segment of the eye. Edaravone and NAC, for example, have not yet shown conclusive results in human clinical trials for retinal neurodegeneration.

3.2 Anti-inflammatory and Immunomodulatory Small Molecules

Inflammation in retinal neurodegeneration is increasingly recognized as more than a secondary response—it can be an active driver of disease progression. Chronic activation of innate immune pathways, microglial reactivity, and sustained cytokine signaling can maintain a hostile retinal microenvironment, impair synaptic function, and exacerbate oxidative injury. Small-molecule immunomodulation therefore aims to "re-balance" inflammatory responses rather than simply suppress them indiscriminately (Zong et al., 2025).

Mechanistically, anti-inflammatory small molecules often target signal transduction hubs that integrate stress cues into cytokine production and immune-cell activation. Such hubs may regulate transcriptional programs, inflammasome activation, or receptor-mediated immune amplification. Because inflammation and oxidative stress frequently reinforce each other, anti-inflammatory candidates are particularly compelling when they also reduce oxidative injury indirectly by dampening inflammatory ROS generation and restoring metabolic stability (Kang

et al., 2021).

Another important rationale for small molecules in this category is their ability to modulate intracellular inflammatory signaling, which is not always accessible to biologics. In principle, this can enable modulation of pathways within microglia, Müller glia, and RPE cells—cell types increasingly implicated in maintaining or disrupting retinal homeostasis during neurodegeneration (Sano et al., 2019).

However, immunomodulation introduces a central translational trade-off: achieving sufficient suppression of damaging inflammation without impairing protective immune functions or creating unacceptable systemic effects, especially under chronic dosing. This trade-off becomes more complex when systemic administration is used, given that retinal exposure may be limited by the blood-retinal barrier while systemic adverse events remain possible (Akaiwa et al., 2017).

Representative candidates and evidence:

Minocycline, a tetracycline antibiotic with anti-inflammatory properties, has shown promise in animal models of optic neuropathy by inhibiting microglial activation and reducing neuronal damage (X. Li et al., 2021).

Corticosteroids, widely used in AMD treatment to control inflammation, have demonstrated short-term efficacy in reducing macular edema, but long-term use is limited by side effects such as elevated intraocular pressure and cataract formation (Cho et al., 2021).

Tocilizumab, an interleukin-6 (IL-6) receptor inhibitor, has been investigated for its potential to mitigate inflammatory damage in AMD and glaucoma by targeting cytokine-mediated inflammatory pathways (Russo et al., 2024).

Despite promising preclinical data, translating these therapies into effective clinical treatments has proven challenging due to concerns about side effects and the need for precise targeting of immune cells in the retina (Sano et al., 2019).

3.3 Neuroprotective Small Molecules Targeting Mitochondria, Apoptosis, and Neuronal Survival Signaling

Neuroprotective small molecules seek to directly preserve retinal neurons by stabilizing core

survival machinery—particularly mitochondrial integrity and regulated cell-death pathways. This category is conceptually closer to "disease modification" because it targets mechanisms that sit near the final common pathway of cell loss.

A primary target domain is mitochondrial stability. Small molecules that preserve mitochondrial membrane potential, improve respiratory efficiency, or support mitochondrial quality control can protect neurons against energy failure and stress-induced apoptosis. Because mitochondrial dysfunction is both a cause and a consequence of oxidative stress and inflammation, mitochondrial-targeted neuroprotection may indirectly dampen multiple degenerative cascades simultaneously (Sun et al., 2025).

A second domain involves apoptosis and regulated cell death pathways. Retinal neurons under chronic stress may activate caspase-dependent apoptosis or related death programs. Small molecules that shift the balance toward survival—either by inhibiting key death-effectors or by reinforcing upstream survival signaling—are theoretically valuable, particularly if administered before irreversible structural collapse. Yet, because cell-death pathways are widely used across tissues, selectivity and delivery become critical; a neuroprotective mechanism must be sufficiently localized to avoid systemic interference with normal cellular turnover or immune functions (Sano et al., 2019).

A third neuroprotective axis concerns neurotrophic and synaptic support, where small molecules may enhance endogenous survival signaling, promote synaptic resilience, or reduce excitotoxic vulnerability. In retinal neurodegeneration, neurons may lose trophic support and experience maladaptive calcium handling or excitatory stress, accelerating degeneration. By stabilizing these neuronal homeostasis mechanisms, neuroprotective molecules aim to "buy time" and preserve function even in the presence of ongoing upstream stressors (Akaiwa et al., 2017).

Representative candidates and evidence:

Cyclosporine A, a potent immunosuppressant, has been shown to stabilize mitochondrial function in retinal neurons and prevent RGC death by inhibiting mitochondrial permeability transition pore (mPTP) opening (Russo et al., 2024).

Fisetin, a natural flavonoid, has demonstrated neuroprotective effects by promoting

mitochondrial biogenesis and inhibiting apoptotic pathways in both retinal and cortical neurons (Kang et al., 2021).

ABT-199, a Bcl-2 family inhibitor, has been studied for its ability to block apoptotic signaling in RGCs, offering potential for protection against cell death due to oxidative stress and inflammatory injury (Harada et al., 2019).

Despite these promising results in preclinical models, challenges remain in ensuring effective retinal delivery and achieving sustained therapeutic concentrations without frequent invasive administration. A summary of these mechanism categories, along with their key targets and translational considerations, is provided in Table 1.

Mechanism category	**Key targets / pathways (examples)**	**Typical outcome measures**	**Translational pros**	**Translational cons / risks**
Antioxidant / Redox-modulating	Nrf2–ARE axis; ROS/RNS scavenging; glutathione homeostasis; NAD^+-related stress resistance (context-dependent)	Oxidative damage biomarkers (lipid/protein/DNA); retinal layer integrity (e.g., OCT/histology); neuronal survival (RGC/photoreceptor counts); functional readouts (ERG, visual behavior)	Addresses a common upstream driver; tunable chemistry may support oral/topical feasibility (compound-dependent); complements anti-inflammatory and neuroprotective strategies	Posterior-segment exposure often short without delivery support; risk of nonspecific "antioxidant" claims without target engagement; may be insufficient as monotherapy when inflammation/mitochondrial failure dominates
Anti-inflammatory / Immunomodulatory	NF-κB signaling; cytokine/chemokine pathways; inflammasome-related signaling (e.g., NLRP3, when relevant); microglial activation and glia–neuron crosstalk	Cytokine profiles; glial activation markers (microglia/Müller/RPE responses); structural preservation (OCT/histology); functional outcomes (ERG, visual behavior)	Targets a key amplifier of degeneration; may indirectly reduce oxidative injury; aligns with multi-target disease-modifying paradigms	Chronic dosing trade-offs (immune balance); systemic off-target effects possible if exposure is nonlocal; must separate true anti-inflammatory action from nonspecific suppression/toxicity
Neuroprotective (mitochondria / apoptosis / survival)	Mitochondrial bioenergetics and membrane stability; mitochondrial dynamics/quality control; apoptosis signaling (caspase pathways, Bcl-2 family balance); calcium dysregulation/excitotoxic stress (context-dependent)	Mitochondrial function readouts (ATP, membrane potential surrogates); apoptosis markers; neuronal survival endpoints; durable functional preservation (ERG, visual behavior; visual field-related surrogates in models)	Acts near the final common pathway of cell loss; stronger potential for true disease modification; can synergize with redox and anti-inflammatory control	Possible narrow safety margins with chronic pathway modulation; high exposure/durability requirements; strong need for PK/PD alignment and long-horizon endpoints

Table 1. Mechanism categories (antioxidant / anti-inflammatory / neuroprotective) mapped to key targets, typical outcome measures, and translational pros/cons

4. Multi-Target Potential and “One Molecule–Multiple Pathways” Strategies

Retinal neurodegenerative diseases are increasingly understood as network disorders rather than single-cause conditions. In glaucoma and AMD, multiple stress-response systems are activated concurrently and reinforce one another over time, creating a self-sustaining degenerative microenvironment. This biological reality motivates the growing interest in multi-target small molecules—agents capable of modulating more than one pathogenic pathway either through pleiotropic mechanisms or coordinated engagement of interconnected targets (Tezel, 2021).

4.1 Why Multi-Targeting Matters in Retinal Neurodegeneration

A central challenge in treating retinal neurodegeneration is the co-occurrence and interdependence of oxidative stress, inflammation, and mitochondrial dysfunction. These processes rarely operate in isolation. Instead, they form a pathological triad in which each component can amplify the others: oxidative stress activates inflammatory signaling and glial reactivity; neuroinflammation generates additional oxidative burden and disrupts metabolic homeostasis; and mitochondrial dysfunction both increases ROS production and lowers the cellular threshold for apoptosis. In such a system, targeting only one pathway may reduce a single "output" marker (e.g., ROS) without meaningfully disrupting the upstream network dynamics that continue to drive neuronal decline (Tezel, 2021).

This motivates a network pharmacology perspective, in which disease progression is viewed as emerging from interactions among multiple nodes and feedback loops. Within complex biological networks, strong inhibition of a single node can be offset by compensatory pathways, redundancy, and adaptive rewiring—phenomena well recognized across chronic degenerative and inflammatory disorders. By contrast, modest but coordinated modulation across several nodes may yield a more durable shift in system behavior, reducing the likelihood that a single compensatory response restores the pathological state. For retinal diseases that evolve over

years and involve heterogeneous patient-specific drivers, a multi-target approach may better match real-world complexity than highly selective single-target strategies (Harada et al., 2019).

Clinically, multi-targeting also aligns with the need for disease modification rather than short-term symptomatic control. If degeneration is sustained by a coupled oxidative–inflammatory–mitochondrial cascade, effective long-term preservation of retinal neurons may require simultaneous reduction of inflammatory toxicity, stabilization of cellular energy metabolism, and prevention of cell-death commitment. Small molecules are particularly attractive in this regard because their chemical flexibility can support multi-pathway activity either intentionally (through design) or functionally (through pathway convergence), preventing programmed cell death (Sano et al., 2019).

4.2 Mechanistic Patterns of Multi-Target Small Molecules

Multi-target small molecules in retinal neurodegeneration commonly exhibit several recurring mechanistic patterns, reflecting the coupled biology of oxidative stress, inflammation, and mitochondrial vulnerability. One prominent pattern is dual antioxidant and anti-inflammatory activity. Because oxidative stress and inflammatory signaling can mutually amplify, compounds that reduce oxidative burden may indirectly attenuate inflammatory activation, and vice versa (Kang et al., 2021; Tezel, 2021). In glaucoma and other optic neuropathy contexts, multi-pathway modulation is frequently framed as a pragmatic response to the limitations of single-mechanism neuroprotection. For example, antioxidant-oriented interventions such as edaravone have been investigated in experimental glaucoma/retinal degeneration models, where reductions in oxidative injury are often accompanied by broader cellular stress attenuation and structural/functional preservation signals (Akaiwa et al., 2017).

A second pattern involves mitochondrial protection coupled with inhibition of apoptosis. Mitochondrial dysfunction is widely discussed as a convergent pathway that links oxidative injury to neuronal death programs, making it an attractive leverage point for multi-domain protection (Harada et al., 2019). In this logic, stabilizing mitochondrial resilience can both

reduce ROS production and raise the threshold for apoptosis activation, thereby providing "upstream–downstream" coverage with a single intervention (Kang et al., 2021; Sun et al., 2025). Consistent with this, redox-supportive strategies that enhance intrinsic antioxidant capacity (e.g., glutathione-related support) are frequently positioned as more durable than simple radical scavenging, because they can influence broader cellular survival programs relevant to mitochondria-associated stress (Kang et al., 2021).

A third pattern is synergistic pathway coverage that limits compensatory feedback. From a network pharmacology perspective, disease progression emerges from coupled feedback loops rather than isolated nodes, so coordinated modulation across oxidative, inflammatory, and survival pathways may yield more durable system-level benefit than strong inhibition of a single target (Sun et al., 2025). This concept has been repeatedly emphasized in glaucoma neuroprotection discussions, where clinical progression despite adequate risk-factor control motivates broader mechanism coverage (Maddineni et al., 2025). In AMD, similarly, the degenerative microenvironment involves intertwined oxidative and inflammatory drivers, supporting the plausibility of multi-target small-molecule strategies.

4.3 Evaluation Principles: Establishing Credible Multi-Target Evidence

Because "multi-target" is an appealing label that can be applied too loosely, rigorous evaluation principles are essential for translational credibility.

First, multi-target claims should be supported by pathway-specific biomarkers demonstrating engagement of each proposed mechanism. For instance, antioxidant activity should be supported by validated oxidative damage readouts or endogenous defense activation signals, while anti-inflammatory activity should be supported by cytokine signaling changes or glial activation state measures, rather than nonspecific stress markers alone (Kang et al., 2021). In glaucoma neuroprotection research, emphasis is often placed on aligning mechanistic biomarkers with meaningful neuronal outcomes to avoid overinterpreting generic "protection" signals.

Second, biomarker improvements must be linked to structural and functional preservation that is relevant to retinal integrity. Multi-target modulation is most persuasive when studies demonstrate convergence among (i) reduced pathological signaling, (ii) preserved neuronal survival or retinal layer integrity, and (iii) improved functional readouts such as electrophysiology or vision-related behavior (Aksar et al., 2015). For example, edaravone-related experimental work is typically interpreted more strongly when oxidative stress reduction coincides with retinal/optic nerve structural protection and measurable functional preservation (Akaiwa et al., 2017).

Third, multi-target evidence should demonstrate dose–response coherence and pharmacological plausibility. True mechanism-based effects commonly show consistent relationships among dose, target-linked biomarkers, and functional outcomes; by contrast, "multi-domain" biomarker suppression observed only at doses that also produce nonspecific toxicity or physiological suppression should be interpreted cautiously. Finally, given the known limitations of disease modeling, strong multi-target arguments are strengthened by cross-model replication and transparent discussion of model constraints, especially when translating neuroprotective signals from animal models to heterogeneous human disease (Harada et al., 2019).

5. Translational Challenges and Limitations

Despite strong mechanistic rationale and expanding preclinical literature, relatively few small-molecule candidates have achieved durable clinical impact in retinal neurodegenerative diseases. This bottleneck reflects interlocking constraints spanning ocular pharmacokinetics, long-term safety, delivery feasibility, and imperfect predictive validity of current models (Akaiwa et al., 2017). The practical consequence is that mechanism strength alone is insufficient, candidates must also achieve sustained posterior-segment exposure with acceptable tolerability and feasible real-world administration (Russo et al., 2024).

5.1 Pharmacokinetic Constraints

A defining challenge for small-molecule therapy in retinal neurodegeneration is sustaining retina-relevant therapeutic exposure in the posterior segment, particularly within relevant compartments, over the long time horizons required for neuroprotection. Even when a compound demonstrates efficacy in acute or subacute models, translation requires that concentrations remain sufficient for target engagement over prolonged periods without impractical dosing frequency (Kulkarni et al., 2025).

Many small molecules exhibit short intraocular half-life and rapid clearance, resulting in limited residence time within the vitreous or surrounding tissues. Clearance can occur through anterior routes (e.g., aqueous humor outflow) or posterior routes (e.g., choroidal blood flow), and the relative contribution depends on molecular properties such as lipophilicity, charge, protein binding, and susceptibility to metabolic enzymes. For diseases that progress slowly, transient exposure may produce only marginal benefits unless dosing is frequent; however, frequent dosing can be unacceptable from both patient and healthcare-system perspectives.

Moreover, maintaining drug levels in the retina/choroid is complicated by tissue partitioning and binding. Compounds may distribute preferentially into off-target ocular compartments, exhibit insufficient penetration to deeper retinal layers, or undergo local metabolism that reduces active drug fraction. These factors create a common translational mismatch: the concentration achieved in accessible compartments (e.g., aqueous humor) may not reliably reflect pharmacologically relevant exposure at the neuronal targets within the retina. Consequently, successful candidates often require either exceptionally favorable intrinsic PK properties or formulation approaches that extend exposure duration and improve posterior segment targeting (Kulkarni et al., 2025).

5.2 Safety and Tolerability

Retinal neurodegeneration typically requires chronic therapy, making safety and tolerability

central to translational viability. Because small molecules can access intracellular pathways central to metabolism and survival, off-target effects are an enduring concern, especially when dosing must be sustained for months to years. In neuroprotection development broadly, the risk–benefit balance becomes particularly sensitive when compounds influence stress-response and survival pathways that are widely used across tissues (Kulkarni et al., 2025).

Ocular tolerability is also critical for long-term use. Candidate therapies must avoid cumulative toxicity that could offset neuroprotective benefits, and delivery-related adverse effects can further shape real-world applicability (Russo et al., 2024). Systemic safety matters as well when delivery routes lead to systemic exposure—an especially relevant concern in older AMD and glaucoma populations with comorbidities and polypharmacy, where drug–drug interactions may complicate chronic administration.

Systemic safety is equally important when treatment routes involve oral administration or significant systemic exposure. Retinal disease patients—especially older adults with AMD or glaucoma—often have comorbidities and are frequently prescribed multiple medications. This increases vulnerability to drug–drug interactions, including effects on hepatic metabolism, transporter systems, and cardiovascular or neurological side effects. Translational development must therefore consider not only intrinsic toxicity but also how a small-molecule candidate will behave in real-world polypharmacy contexts over prolonged treatment periods.

5.3 Delivery Barriers and Real-World Adherence

Delivery is often the practical gatekeeper determining whether mechanistically plausible therapies can become clinically implementable. Across retinal disease contexts, limitations in achieving sustained posterior exposure through noninvasive routes contribute substantially to translational attrition (Russo et al., 2024). While local administration can increase posterior concentrations, frequent invasive dosing increases treatment burden and may negatively affect long-term adherence—an issue repeatedly emphasized in glaucoma neuroprotection and chronic retinal therapy discussions.

Each major administration route carries trade-offs. Topical delivery is attractive because of convenience and patient acceptance, but most compounds achieve low posterior segment concentrations, and consistent dosing over long periods can be challenging. Systemic delivery may be feasible for some highly permeable molecules, yet retinal exposure can remain limited by the BRB while systemic side effects and interactions persist. Intravitreal injection can deliver high posterior segment concentrations, but repeated injections increase treatment burden and cumulative complication risk and may reduce adherence over time.

Adherence is particularly consequential in chronic retinal diseases because neurodegeneration is gradual and symptoms may not be immediately apparent to patients until progression becomes advanced. This can reduce motivation for sustained treatment, especially when dosing regimens are frequent or invasive. Therefore, translational success depends not only on pharmacology and safety but also on whether the delivery strategy is compatible with long-term patient behavior and healthcare delivery capacity. In this context, approaches that reduce dosing frequency, simplify administration, and maintain stable retinal exposure are likely to have a disproportionate impact on real-world effectiveness.

5.4 Preclinical-to-Clinical Gaps

A persistent limitation in retinal neurotherapeutics is the imperfect predictive validity of current preclinical models. While animal and cellular systems enable mechanistic dissection, they cannot fully reproduce human disease heterogeneity, aging biology, or long-duration progression patterns that shape clinical outcomes (Harada et al., 2019). This is particularly relevant to glaucoma and AMD, where patient subtypes may differ in dominant drivers (e.g., inflammatory vs. metabolic vs. vascular components), diluting average treatment effects unless stratification approaches are applied (Shah et al., 2019).

Disease heterogeneity further complicates translation. Patients differ in genetic background,

comorbidities, environmental exposures, baseline retinal reserve, and dominant mechanistic drivers (e.g., inflammation-dominant vs. vascular-dominant phenotypes). A therapy that appears effective in a relatively homogeneous preclinical context may show diluted or variable effects in heterogeneous clinical populations unless appropriate stratification strategies are adopted.

Finally, there is a continuing need for standardized and clinically meaningful endpoints that align preclinical results with patient benefit. Structural endpoints (e.g., retinal layer integrity), functional endpoints (e.g., electrophysiology, visual field measures), and patient-reported outcomes each capture different dimensions of disease impact. Without consistent cross-study standards, it becomes difficult to compare candidates or to interpret whether biomarker improvements are likely to translate into meaningful vision preservation. A robust translational pipeline therefore requires harmonized outcome frameworks and careful selection of endpoints that reflect both disease biology and patient-relevant function over appropriate timescales.

6. Future Perspectives: Nanotechnology-Enabled Delivery as a Highlight

The translational limitations summarized in Section 5—short intraocular residence time, subtherapeutic posterior segment exposure, and the practical burden of chronic administration—are not merely "formulation problems," but structural barriers that critically impact the clinical success of even mechanistically strong small molecules. In this context, nanotechnology-enabled delivery is increasingly viewed as a strategic enabler: rather than changing the therapeutic mechanism itself, nanocarriers can reshape ocular pharmacokinetics, improve tissue distribution, and reduce treatment burden, thereby increasing the likelihood that neuroprotective effects observed in experimental systems translate into real-world benefit (Tang et al., 2025).

6.1 Why Nanocarriers for Small Molecules

Nanocarriers are particularly well matched to small-molecule development in retinal neurodegeneration for three primary reasons.

First, they can improve ocular bioavailability and retinal targeting. Many small molecules have suboptimal solubility, rapid clearance, or unfavorable partitioning into non-target ocular compartments. Encapsulation can protect the payload, enhance solubilization of lipophilic compounds, and—depending on surface properties, promote distribution toward posterior tissues. This is especially important for agents intended to act on retinal neurons, glia, or RPE cells, where free-drug exposure is often limited by multiple anatomical barriers (Akaiwa et al., 2017; Russo et al., 2024).

Second, nanocarriers can enable sustained release, directly addressing the short half-life and rapid clearance that commonly limit small-molecule durability. Sustained release is not a convenience feature; in chronic neurodegeneration, it can be mechanistically meaningful because maintaining stable exposure may prevent repeated cycles of stress activation and reduce the probability that neurons cross irreversible thresholds for apoptosis or functional collapse (Akaiwa et al., 2017; Russo et al., 2024).

Third, nanotechnology can reduce dosing frequency and potentially mitigate side effects. By increasing local ocular exposure while lowering systemic spillover, a delivery system can improve the therapeutic index—achieving effective retinal concentrations without proportionally increasing systemic exposure. In turn, reduced dosing frequency can improve adherence and reduce cumulative procedural risk, particularly for delivery routes that otherwise require repeated intravitreal injections (Tang et al., 2025).

6.2 Nanotechnology Strategies for Ocular Delivery

A practical review framework focuses on platform families targeting distinct but overlapping objectives: solubility/penetration, controlled release, prolonged residence, and targeted cellular uptake. These systems offer several advantages over traditional drug delivery methods, as illustrated in Figure 2.

(1) Lipid-based nanoparticles and nanomicelles (solubility + penetration support)

Lipid-based systems and nanomicelles are often used to improve the apparent solubility of hydrophobic small molecules and enhance their transport across ocular barriers. Their amphiphilic architecture can stabilize poorly soluble drugs and promote interaction with biological membranes, which may be advantageous for improving local tissue exposure. In retinal neurodegeneration, such systems are especially relevant when the limiting factor is not potency but insufficient drug reaching the posterior segment. Conceptually, these carriers aim to "unlock" the pharmacology of a candidate by ensuring the molecule is present where it needs to act.

(2) Polymeric nanoparticles (controlled release + protection of payload)

Polymeric nanoparticles are frequently positioned as controlled-release platforms. By modulating polymer composition and degradation kinetics, these systems can provide extended drug release profiles tailored to chronic diseases. For retinal neurodegeneration, polymeric carriers are attractive because they can support longer dosing intervals and stabilize exposure, which may be critical for maintaining continuous modulation of oxidative, inflammatory, or mitochondrial pathways. In addition, polymeric matrices can protect labile molecules from premature degradation, preserving active drug fraction and improving PK/PD consistency.

(3) Hydrogels and in situ gels (prolonged ocular residence + depot effect)

Hydrogel-based systems, including in situ gelling formulations, can create a local depot that increases retention time at the site of administration. Their value is particularly clear for strategies that seek prolonged presence in ocular compartments—either to extend release following periocular administration or to enhance local retention in topical contexts. In a translational sense, gels are often framed as adherence- and feasibility-oriented technologies: by enabling sustained local delivery with fewer administrations, they can reduce patient burden and stabilize long-term exposure patterns.

(4) Targeting ligands (optional advanced direction: cell- or tissue-preferential uptake)

A more advanced approach involves functionalizing nanocarriers with targeting ligands to promote preferential uptake by specific retinal cell types (e.g., RPE, microglia) or to enhance transport toward particular tissues. While this strategy is conceptually powerful—especially for multi-target neuroprotection where cell-type specificity might reduce off-target effects—it also increases development complexity. For review purposes, targeting is best presented as an emerging direction that requires strong justification, clear evidence of improved cellular delivery, and careful evaluation of immunogenicity and manufacturing reproducibility.

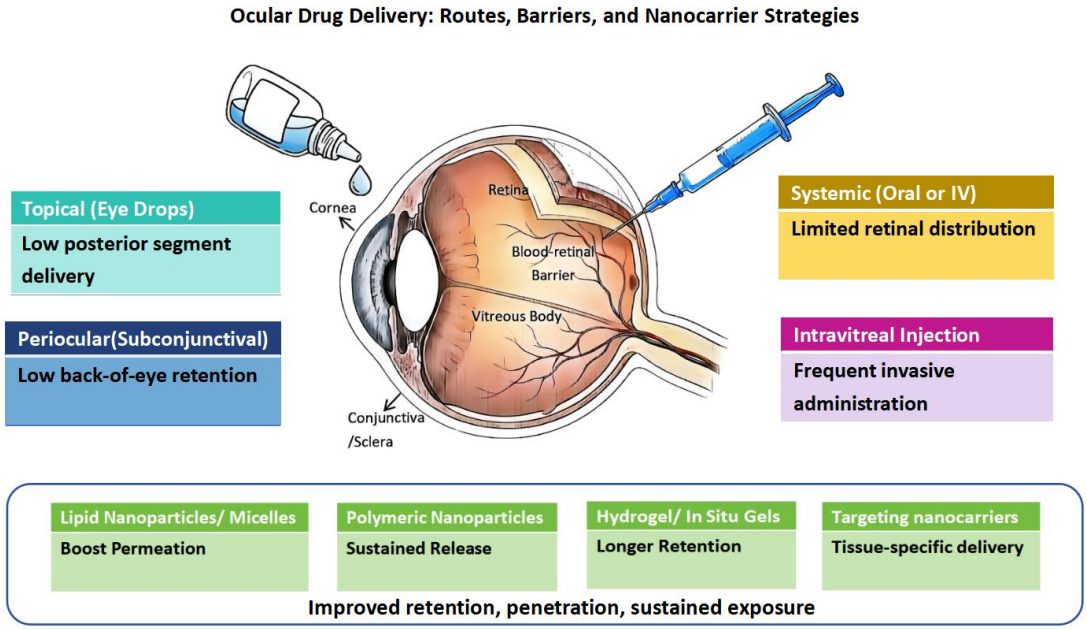

Figure 2. Delivery routes and ocular barriers, and where nanocarriers improve retention/penetration and sustained exposure

6.3 Key Design Considerations

The translational viability of nanocarriers depends on whether engineering choices align with ocular biology, safety requirements, and regulatory expectations. Several design dimensions are consistently decisive.

Physicochemical parameters (size, surface charge, stability, loading efficiency). Particle size and surface properties strongly influence distribution, barrier interaction, clearance pathways, and cellular uptake. Stability matters not only for shelf life but also for ensuring predictable

release kinetics in vivo. Drug loading efficiency and release profiles must be optimized in ways that preserve therapeutic concentrations without inducing burst release that could elevate toxicity risk (Russo et al., 2024).

Sterility, biocompatibility, and regulatory feasibility. Ocular products demand high sterility standards and strict tolerability. A delivery platform that is mechanistically elegant but difficult to sterilize, prone to aggregation, or associated with inflammatory responses will face steep barriers to clinical adoption. Biocompatibility must be evaluated in both short-term and chronic contexts, given the long treatment horizons typical of retinal neurodegeneration (Akaiwa et al., 2017).

Manufacturing scalability and reproducibility. Many nanotechnologies fail at the "translation interface" not due to lack of efficacy, but due to inconsistent batch-to-batch properties or manufacturing processes that cannot be scaled. For clinical relevance, the platform must support reproducible particle characteristics and stable release behavior under scalable production methods.

Taken together, these considerations argue for an engineering philosophy in which nanocarrier development is not an afterthought appended to a drug candidate, but a parallel, co-optimized process designed to stabilize exposure, improve localization, and reduce practical burden.

6.4 Proposed Research Roadmap

To accelerate translation, a structured development pathway is helpful—one that aligns candidate selection, delivery engineering, and evidence generation.

Step 1: Prioritize lead compounds with strong mechanistic rationale and safety margins.

Candidates should demonstrate coherent mechanism-to-function relationships in relevant models, with early signals of tolerability under repeated dosing. Because delivery systems can amplify exposure, compounds with narrow safety windows may become less viable unless targeting and release kinetics can reliably constrain peak concentrations (Russo et al., 2024).

Step 2: Pair lead compounds with delivery platforms early (co-development).

Rather than optimizing the molecule first and "adding delivery later," co-development allows PK constraints to inform chemistry and formulation choices. Early PK studies should focus on whether the platform achieves sustained retinal exposure and target-relevant distribution, not merely higher overall ocular concentrations (Kulkarni et al., 2025; Tang et al., 2025).

Step 3: Build a translational evidence package integrating PK/PD, toxicity, and functional outcomes.

A strong package typically includes: (i) posterior-segment PK profiles, (ii) PD biomarkers linked to oxidative stress, inflammation, mitochondrial function, or apoptosis modulation, (iii) ocular and systemic toxicity under chronic dosing paradigms, and (iv) functional endpoints that approximate clinically meaningful vision preservation (Kulkarni et al., 2025; Mimura & Noma, 2025; Tang et al., 2025; Zong et al., 2025).

Step 4: Design trials and endpoints that reflect durability and patient relevance.

Because retinal neurodegeneration unfolds slowly, development programs should emphasize sustained structural and functional preservation and incorporate patient-centered outcomes where feasible. Delivery platforms that reduce dosing burden may also improve adherence, which should be considered as part of real-world effectiveness rather than a peripheral implementation issue (Akaiwa et al., 2017).

7. Conclusion

Retinal neurodegenerative diseases such as glaucoma and AMD remain leading causes of irreversible vision loss, underscoring the need for therapies that move beyond symptomatic control toward genuine disease modification and neuroprotection. Small-molecule drugs offer important advantages, including tunable permeability, intracellular target access, scalable production, and flexibility for combination or multi-target strategies. Mechanism-based classes—antioxidant/redox modulators, anti-inflammatory or immunomodulatory agents, and neuroprotective molecules targeting mitochondrial and apoptotic pathways—collectively define a rich pipeline of therapeutic concepts. In parallel, the network biology of retinal

degeneration supports the rationale for multi-target approaches, in which coordinated modulation across oxidative stress, inflammation, and mitochondrial dysfunction may outperform single-pathway inhibition in chronic, heterogeneous disease.

However, clinical translation is constrained by pharmacokinetic limitations, long-term safety requirements, delivery barriers, and preclinical–clinical mismatches. A central message emerging from these challenges is that pharmacology alone is insufficient; even strong mechanisms can fail without durable posterior-segment exposure and feasible long-term administration. In this light, integrating rational small-molecule design with nanotechnology-enabled delivery is not merely a technical refinement but a potentially pivotal strategy for achieving sustained retinal exposure, reducing dosing frequency, improving adherence, and ultimately enabling clinically meaningful neuroprotection in retinal neurodegenerative disorders.

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