

# Recent Progress in Selenium Nanomedicines for Ocular Diseases

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**Abstract:** Vision impairment represents a significant and growing global socioeconomic burden. In the elderly population, cataracts, age-related macular degeneration (AMD), glaucoma, and diabetic retinopathy (DR) are the predominant causes of visual loss. Conventional ophthalmic drug therapies are limited by low bioavailability and dose-related toxicity, highlighting the urgent need for safer and more effective treatments. Selenium (Se), an essential trace element, is critical for antioxidant defense, redox homeostasis, and immune regulation. Although the roles of elemental Se in ocular physiology and diseases are well-documented, its clinical application is constrained by its narrow therapeutic window and poor bioavailability. To overcome these limitations, Se nanoparticles (SeNPs) have emerged as a superior alternative, offering enhanced bioavailability, reduced toxicity, and the capability for targeted drug delivery. Strong preclinical evidence supports the therapeutic potential of Se nanomedicines in models of DR, retinal neovascularization, infectious keratitis, and cataracts. Significantly, the initial stages of clinical translation are in progress, as demonstrated by a pioneering Phase I trial involving CdSe/ZnS quantum dots (QDs) in patients with retinitis pigmentosa (RP), which has shown both tolerability and improvements in visual function. This review provides a comprehensive and up-to-date analysis of Se-based nanomedicines for ocular diseases, based on a literature search of PubMed, Scopus, Web of Science, and Google Scholar. It elucidates how SeNPs uniquely synergize intrinsic multi-mechanistic bioactivities (e.g., antioxidant, anti-angiogenic) with targeted and stimuli-responsive drug delivery, establishing them as versatile nanoplatforms with significant clinical translation potential for complex ocular pathologies. Therefore, further research is essential to optimize their design, elucidate their mechanisms of action, and ultimately facilitate their safe and effective clinical translation.

**Keywords:** ocular diseases, selenium nanoparticles, selenium, nanotechnology, oxidative stress

## Introduction

Global vision impairment is a pressing public health challenge, affecting over 2.2 billion people worldwide according to the World Health Organization in 2019.<sup>1</sup> This burden is exacerbated by population growth, aging, and inequitable access to care, necessitating coordinated global intervention. Among the elderly, cataracts, age-related macular degeneration (AMD), glaucoma, and diabetic retinopathy (DR) are the leading causes of visual impairment.<sup>1,2</sup> The pathological mechanisms of these diseases are primarily driven by oxidative injury, inflammatory dysregulation and impaired autophagy.<sup>3</sup> Conventional ophthalmic drug therapies face multiple challenges, such as compromised bioavailability due to anterior segment barriers (e.g., rapid tear clearance, the cornea) and posterior segment barriers (e.g., the blood-retinal barrier), dose-dependent local and systemic toxicity, and poor patient compliance caused by frequent dosing. Furthermore, invasive intravitreal injections carry risks of endophthalmitis and elevated intraocular pressure. These limitations highlight the urgent need for novel therapeutic strategies with improved efficacy and safety.<sup>4</sup>

Nanomedicine offers a powerful approach to overcome these challenges by employing a wide array of nanomaterials. These include organic carriers (e.g., liposomes, polymer micelles, dendrimers), inorganic particles (e.g., metal nanoparticles, quantum dots (QDs), mesoporous silica), and biologically derived components (e.g., exosomes, natural polysaccharides). Such nanocarriers can effectively navigate the complex physiological barriers of the eye and have shown significant potential in treating various ocular diseases, including dry eye disease (DED), keratitis, glaucoma, uveitis, AMD, DR, and retinal vascular occlusion (RVO). They enhance drug stability, bioavailability, and targeting capabilities, thereby improving ocular absorption, extending retention time, and reducing dosing frequency. Beyond serving as advanced delivery vehicles, many nanomaterials exhibit inherent therapeutic and diagnostic (theranostic) properties, such as antioxidant, antimicrobial, and imaging functions. This multifunctional integration positions nanomedicine as a transformative strategy for advancing clinical outcomes in ophthalmology.<sup>4–6</sup>

Among these, Se-based nanomedicines have attracted considerable attention due to the inherent bioactivity of Se, as an essential trace element. Se is integrated into selenocysteine (Sec) and utilized by at least 25 human selenoproteins. These proteins function primarily as potent redox enzymes, playing crucial roles in antioxidant defense, thyroid hormone metabolism, and endoplasmic reticulum protein quality control.<sup>7,8</sup> However, conventional Se forms are constrained by a narrow therapeutic window and poor absorption. Se deficiency, affecting 0.5 to 1 billion people worldwide, is linked to various disorders, including several ocular pathologies such as Graves' Orbitopathy (GO), keratoconus, age-related cataract (ARC), DR, decreased distance visual acuity, and glaucoma.<sup>8–19</sup> Conversely, excessive Se intake is associated with carcinogenesis, cytotoxicity, and genotoxicity.<sup>20</sup> In contrast, selenium nanoparticles (SeNPs) demonstrate superior absorption, enhanced bioactivity, reduced toxicity, and targeted drug delivery, overcoming the limitations of conventional forms.<sup>21,22</sup>

As an emerging nanotheranostic platform, SeNPs demonstrate significant potential across the biomedical field. Therapeutically, they exhibit remarkable anticancer, antimicrobial, antiviral, antioxidant, and anti-inflammatory activities. They can selectively target cancer cells by inducing reactive oxygen species (ROS) generation, and serve as efficient carriers for chemotherapeutic drugs, genes, and other therapeutics, enhancing efficacy while reducing systemic toxicity.<sup>20,23–25</sup> Diagnostically, they are utilized in advanced biosensing and bioimaging applications due to their unique enzyme-mimetic and optical properties, such as in constructing sensitive sensors for hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) or acting as contrast agents.<sup>20,24,26</sup>

The successful development of SeNPs in broader biomedical fields has prompted their investigation in ophthalmic nanomedicine, where they show particular promise for treating vision-threatening diseases including DR, retinal neovascularization, and keratitis.<sup>27–29</sup> However, a comprehensive review that critically examines the relationship between the rational design of SeNPs and their specific therapeutic mechanisms and applications across various ocular pathologies remains absent. This review addresses this gap by providing a comprehensive analysis of recent progress in Se-based nanomedicines for ocular diseases. It begins with a concise overview of Se metabolism and its relevance to ocular physiology and pathology, then details the rational design of SeNPs, including their synthesis, key properties, and functionalization strategies. The central focus is a detailed analysis of the therapeutic mechanisms and applications of these nanomedicines across various ocular pathologies, concluding with a discussion of translational challenges and future directions in precision nanomedicine.

## Selenium and Selenoproteins

### Metabolism and Biological Functions of Selenium

While the Se content in food varies considerably,<sup>8</sup> its absorption, distribution, metabolism, and excretion are highly dependent on whether it is ingested in organic or inorganic forms.<sup>30</sup> For incorporation into selenoproteins, all dietary Se must first be metabolized into the central precursor, hydrogen selenide (H<sub>2</sub>Se). Inorganic species like selenite are reduced to H<sub>2</sub>Se primarily via glutathione (GSH) or thioredoxin (Trx)-dependent pathways. In contrast, organic compounds such as selenomethionine are metabolized to Sec through trans-selenation reactions, which is subsequently cleaved by Sec lyase (SCLY) to release H<sub>2</sub>Se.<sup>31</sup> Selenophosphate synthetases (e.g., SPS2) then utilize H<sub>2</sub>Se to generate selenophosphate

( $\text{H}_2\text{SePO}_3^-$ ), the active Se donor. A unique, highly conserved co-translational mechanism involving a specific tRNA (tRNA[Ser]Sec) enables the direct incorporation of pre-synthesized Sec into selenoproteins.<sup>32</sup>

The distinct metabolic pathways for organic and inorganic Se underpin their differing pharmacokinetics (PK). Organic Se compounds exhibit high absorption (>90%) via amino acid transporters, as demonstrated in both animal and human studies.<sup>33,34</sup> They are nonspecifically incorporated into tissue proteins (e.g., muscle, liver), forming mobilizable reserves with a long half-life, which enables gradual release, as supported by human evidence.<sup>34</sup> Unabsorbed portions are excreted in feces. In contrast, inorganic Se in humans exhibits lower, more variable absorption (20–70%) via passive diffusion or sulfate transporters, and is rapidly metabolized. It is either utilized for selenoprotein synthesis or excreted within 1–3 days as dimethylselenide (via breath) or trimethylselenonium (in urine).<sup>34</sup> Consequently, the sustained retention of organic Se confers approximately twofold higher bioavailability as demonstrated in a rat model and lower acute toxicity than rapidly cleared inorganic forms, establishing it as the preferred form for long-term supplementation.<sup>35</sup>

The biological significance of Se is realized through its incorporation into ~25 selenoproteins, which are primarily potent redox enzymes. The main families include (i) Glutathione peroxidase (GPX), where Se-dependent isoforms (GPX1–4, GPX6) reduce hydroperoxides and lipid peroxides, and cysteine-based isoforms (e.g., GPX5, GPX7, GPX8) participate in redox signaling and immune modulation; (ii) Iodothyronine deiodinases (DIO1–3), which control thyroid hormone activity by converting thyroxine ( $\text{T}_4$ ) to the active triiodothyronine ( $\text{T}_3$ ) or the inactive reverse  $\text{T}_3$  ( $\text{rT}_3$ ); and (iii) Thioredoxin reductases (TrxRs; TXNRD1–3), which sustain thioredoxin redox cycles to regulate cellular redox homeostasis and support transcription factor activation.<sup>8,20</sup>

## The Role of Selenium in Ocular Physiology and Disease

Se is crucial for maintaining ocular redox balance and visual function, with its distribution across ocular tissues reflecting regional antioxidant demand. McGahan et al quantified Se in human ocular tissues (0.23–0.41  $\mu\text{g/g}$ ), noting that aqueous humor levels were substantially lower than in plasma, indicating the presence of a selective ocular barrier.<sup>36</sup> Complementing these distribution studies, Ugarte et al used synchrotron X-ray microscopy to locate Se in the mouse choriocapillaris and retinal pigment epithelium (RPE). High-resolution imaging further revealed distinct Se-rich spherical structures at the photoreceptor-RPE interface. Although this technique cannot define chemical speciation, the authors propose these structures likely represent selenium-protein complexes, suggesting specific roles in phagocytosis or trans-RPE transport.<sup>37</sup> Functionally, Se deficiency in rats reduced ocular GPX activity by 27% and exacerbated cadmium-induced lipid peroxidation, providing direct evidence for its critical role in defending against oxidative stress.<sup>38</sup>

On the ocular surface, Se critically regulates corneal health through antioxidant (e.g., tear selenoprotein P), anti-inflammatory, and reparative pathways.<sup>39</sup> Therapeutic applications underscore this role, for instance, topical application of 0.01 g/L Se with vitamin E (Vit E) accelerates corneal ulcer healing by mitigating oxidative stress,<sup>40</sup> while the organo-Se compound ebselen effectively targets fungal keratitis by selectively disrupting fungal thioredoxin system.<sup>41</sup> Furthermore, Se-binding lactoferrin and selenoprotein P alleviate dry eye by suppressing inflammatory mediators and oxidative damage,<sup>42–44</sup> and 0.5% Se sulfide improves symptoms in meibomian gland dysfunction.<sup>45,46</sup> Beyond endogenous molecules, organo-Se coatings on ophthalmic materials can inhibit bacterial colonization with >99.9% efficacy without corneal toxicity.<sup>47–49</sup>

Epidemiological evidence further links systemic Se status to visual function. One study found hair Se levels were 1.5-fold higher in boys than girls among myopic subjects.<sup>50</sup> Research in an Amazonian population demonstrated that higher plasma Se is associated with improved visual contrast sensitivity, while Se deficiency increases susceptibility to color vision loss. This impairment is exacerbated by mercury exposure, which reduces plasma Se and eicosapentaenoic acid levels.<sup>51</sup>

In the lens, Se plays a protective role against ARC. Maintaining serum Se between 75–85  $\mu\text{g/L}$  is associated with a reduced risk of ARC.<sup>52</sup> Pseudoexfoliation syndrome has been linked to local Se deficiency, and selenomethionine supplementation (100  $\mu\text{g/day}$ ) has been shown to reduce lens epithelial apoptosis by 41%.<sup>53</sup> The protective mechanism primarily involves the activation of GPX to alleviate oxidative damage. However, this beneficial effect is dose-

dependent, as supratherapeutic doses can inhibit DNA synthesis and disrupt GSH metabolism via  $\gamma$ -glutamylcysteine synthetase ( $\gamma$ -GCS) inhibition.<sup>54,55</sup> Se also modulates the Hg/Se ratios, attenuating mercury-related ARC risk.<sup>17</sup>

Se exhibits a dual role in glaucoma pathophysiology. Systemic overload or dietary excess increases disease risk, whereas moderate levels in the aqueous humor may be protective. This toxicity mechanism involves Se-induced dysfunction of the trabecular meshwork, characterized by cytoskeletal collapse, impaired phagocytosis, and extracellular matrix dysregulation, which obstructs aqueous outflow. An age-related decline in aqueous Se levels may further exacerbate susceptibility.<sup>56–59</sup>

In GO, clinical trials have demonstrated the therapeutic benefit of Se. Supplementation with 100–200  $\mu$ g/day over six months significantly improves the clinical activity score, reduces proptosis, and enhances the quality of life in patients with mild GO.<sup>60,61</sup> These clinical benefits are associated with reduced levels of thyrotropin receptor antibodies (TRAb) and antioxidant-mediated suppression of orbital inflammation.<sup>62,63</sup>

The effects of Se on the posterior segment are complex and multifaceted. Selenomethionine has been shown to activate the Nrf2/SLC7A11 pathway in cultured RPE cells, increasing GSH levels and mitigating oxidative damage in models of retinal aging.<sup>64</sup> Paradoxically, under conditions of Vit E deficiency, Se can worsen retinal structural damage induced by hyperbaric oxygen.<sup>65</sup> In Behçet's disease, patients exhibit diminished serum Se levels,<sup>66</sup> and the presence of autoantibodies against Se-binding protein 1 (SBP1) is associated with more severe uveitis.<sup>67</sup> Se accumulation in the choroid-RPE of donors with late-stage AMD, compared to controls, may indicate either a compensatory response or a pathological process.<sup>68</sup> In DR, higher Se dietary intake is linked to a reduced disease risk;<sup>69</sup> however, patients with advanced DR show lower Se levels in plasma and vitreous humor, suggesting that deficiency may exacerbate oxidative stress and contribute to progression.<sup>70</sup> Prolonged combined deficiencies of Se and Vit E can lead to the deposition of fluorescent pigments in the RPE, a pathology resembling retinal degeneration.<sup>71</sup>

## Limitations of Elemental Selenium

The toxicity profile of Se is critically dependent on its chemical form and dosage. Inorganic species are generally more acutely toxic than organic ones. In humans, acute poisoning results in systemic weakness and neurological impairment. Chronic overexposure, meanwhile, is associated not only with gastrointestinal distress but also with adverse neurological effects.<sup>72</sup> In zebrafish models, organic Se bioaccumulates, and chronic exposure can inhibit GPX activity, inducing ferroptosis and apoptosis, which explains observed ocular developmental defects and transgenerational visual impairment.<sup>73–75</sup> In contrast, inorganic Se exerts acute toxicity through the Fenton reaction, generating harmful ROS.<sup>30</sup> The poor bioavailability and nonspecific biodistribution of these conventional Se forms compromise targeted selenoprotein activation. These inherent limitations provide a compelling rationale for the development of SeNPs, wherein rational design enables size-modulated transport and receptor-targeted delivery. This advanced strategy successfully expands the therapeutic window while mitigating the toxicity risks associated with elemental Se.<sup>30,73,75</sup>

## Physicochemical Properties and Pharmacokinetics of SeNPs

The biological behavior and therapeutic efficacy of SeNPs are governed by a complex interplay of physicochemical properties, among which size is particularly critical. Size directly influences cellular uptake mechanisms, as endocytosis is most efficient for nanoparticles smaller than 50 nm in key ocular cell types, such as human corneal epithelial cells and retinal tissues.<sup>76,77</sup> This principle is paramount in ocular drug delivery, where size dictates tissue distribution and penetration. For example, following intravitreal injection, nanoparticles  $\geq 100$  nm typically remain dispersed within the vitreous humor, while those around 50 nm can traverse the retinal barrier and accumulate in retinal tissues.<sup>77</sup> Furthermore, smaller nanoparticles are more susceptible to rapid clearance via lymphatic drainage and choroidal blood flow, whereas larger particles ( $>100$  nm) generally exhibit prolonged retention and circulation within ocular compartments.<sup>5</sup> Achieving effective ocular surface delivery thus requires a precise balance between tissue penetration and residence time. Beyond biodistribution, the high surface-area-to-volume ratio of smaller nanoparticles enhances their intrinsic bioactivity and biomolecular interactions.<sup>22</sup> This is exemplified by the finding that 35 nm SeNPs inhibit cancer cell proliferation 1.6-fold more effectively than 91 nm SeNPs, primarily due to enhanced ROS-mediated cytotoxicity.<sup>78</sup>

In addition, other parameters, including surface charge, lipophilicity, shape, and degradation rate and byproducts, critically influence nanoparticle fate and function.<sup>5</sup>

A primary challenge in leveraging these properties is the innate instability of unmodified SeNPs, which aggregate into inert, black clusters due to high surface energy, severely compromising their bioactivity.<sup>25</sup> Surface engineering addresses this limitation. Stabilization with amino- or hydroxyl-group ligands (e.g., chitosan) promotes the formation of mono-disperse spheres via electrostatic repulsion, thereby improving colloidal stability, extending corneal retention, and reducing acute toxicity.<sup>5,22</sup> Further functionalization with targeting ligands (e.g., RGD peptides) enables receptor-mediated endocytosis, significantly enhancing drug accumulation in specific ocular tissues like the cornea and retina.<sup>79</sup> Moreover, engineering SeNPs with stimuli-responsive materials facilitates controlled drug release in pathological microenvironments; for instance, pH-responsive systems target acidic niches (e.g., the tumor microenvironment), while redox-responsive designs leverage elevated ROS levels to trigger release, enhancing therapeutic precision.<sup>80,81</sup> The intrinsic bioactivity of SeNPs, combined with their drug-carrying capacity, allows for synergistic effects with modalities like chemotherapy and photodynamic therapy, positioning them as versatile platforms for combination therapy.<sup>24,25</sup>

The pharmacokinetic profile of SeNPs is administration-dependent. Upon oral administration, SeNPs encounter the gastrointestinal environment, where they rapidly adsorb biomolecules to form a protein corona that dictates subsequent intestinal absorption and systemic biodistribution. Following cellular uptake via endocytosis, intracellular GSH reduces the SeNPs to bioactive metabolites, such as H<sub>2</sub>Se, which serves as the key precursor for Sec biosynthesis. The subsequent incorporation of Sec into selenoproteins like GPX enhances the cellular antioxidant defense system (Figure 1).<sup>20</sup> Systemic clearance is governed by size, surface coating, and protein corona. Particles smaller than the renal filtration threshold (~5–6 nm) are rapidly excreted by the kidneys, while larger or polyethylene glycol (PEG)-modified nanoparticles exhibit prolonged circulation and are processed via the hepatobiliary system, often with transient accumulation in mononuclear phagocyte system (MPS) cells such as Kupffer cells.<sup>82,83</sup> Consequently, strategic surface engineering is a validated approach to modulate the PK and direct the clearance pathway of SeNPs.<sup>84</sup>

SeNPs demonstrate enhanced biosafety compared to conventional Se forms, as evidenced by a sevenfold increase in the acute median lethal dose (LD<sub>50</sub>) relative to selenite, alongside an absence of hepatotoxicity and growth inhibition.<sup>85</sup> In subacute toxicity evaluations, SeNPs induced no histopathological alterations and maintained normal serum biomarker levels, while simultaneously enhancing hepatic antioxidant enzymes, such as superoxide dismutase (SOD), GPX, catalase (CAT), and glutathione S-transferase (GST), and mitigating genotoxicity.<sup>21</sup> The safety profile of SeNPs is concentration-dependent, demonstrating efficacy without cytotoxicity at low concentrations (10–20 µg/mL) in zebrafish models, with adverse effects emerging only at elevated concentrations (30–50 µg/mL).<sup>86</sup>

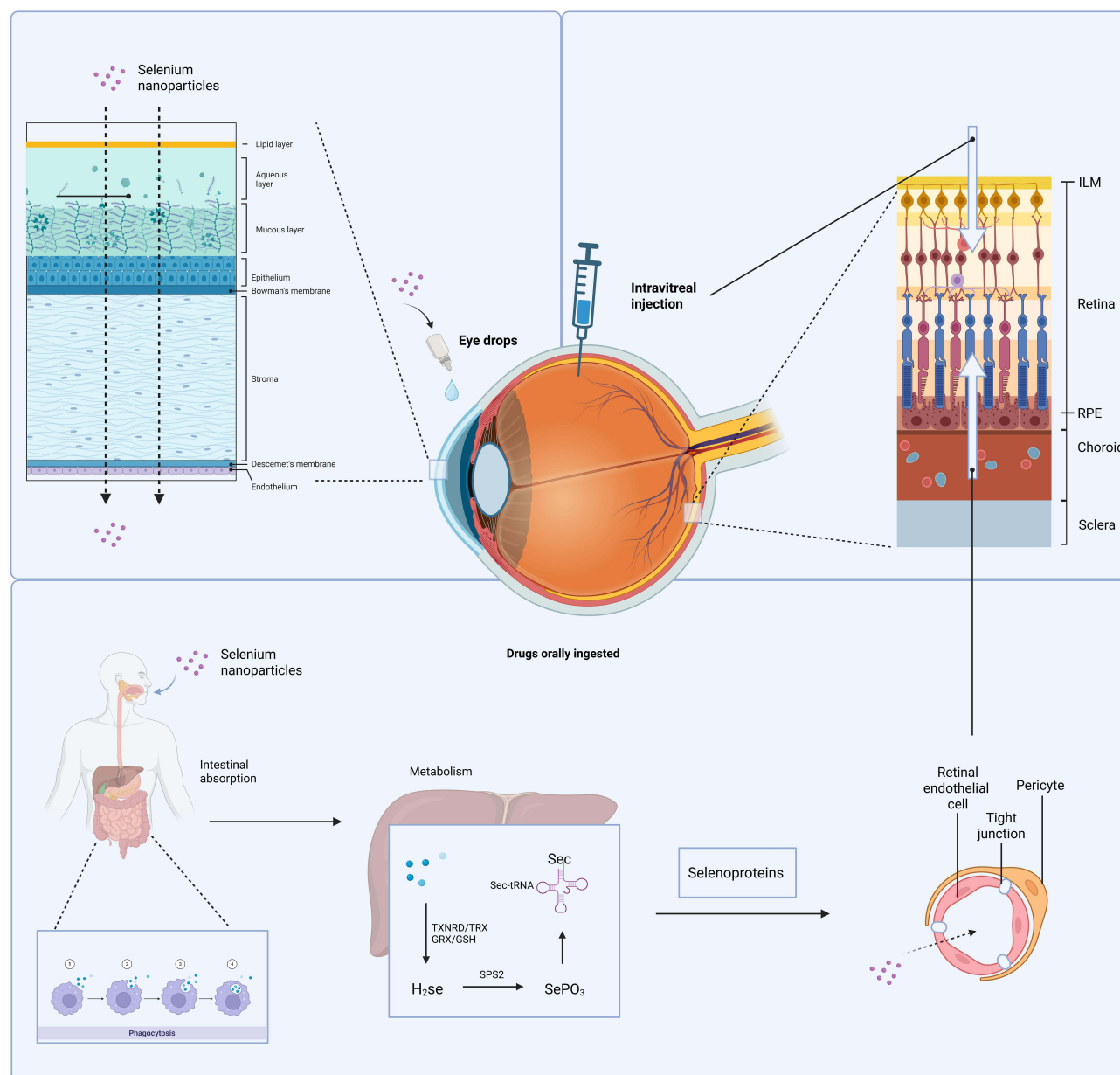
## Functional Design and Synthesis of SeNPs

The synthesis methodology dictates the physicochemical characteristics of SeNPs. Current strategies are grouped into physical, chemical, and biological methods, each with distinct advantages and limitations.

Physical techniques, including pulsed laser ablation (PLA), vapor deposition, and microwave/laser irradiation, enable the production of high-purity SeNPs. For instance, PLA generates spherical particles (3–900 nm) with excellent colloidal stability that are readily collected via centrifugation. However, these methods require specialized instrumentation and precise control of operational parameters (e.g., laser wavelength, energy input, duration), which limits their scalability and widespread adoption.<sup>87</sup>

Chemical reduction remains the most prevalent approach, employing reductants (e.g., ascorbic acid, glutathione) and stabilizers (e.g., bovine serum albumin, carboxymethyl cellulose) to convert inorganic Se precursors into SeNPs. A significant drawback of this method is the persistent presence of residual reagents that resist complete removal through standard purification, introducing potential cytotoxicity and immunogenicity that can impede biomedical applications.<sup>27,87–89</sup>

In contrast, biosynthesis utilizing microorganisms, plant extracts, or enzymatic systems, converts Se precursors into SeNPs under mild, environmentally benign conditions. Naturally occurring biomolecules (e.g., proteins, polysaccharides) serve as *in situ* capping and stabilizing agents, enhancing both biocompatibility and colloidal stability. This green synthesis approach presents a compelling alternative to energy-intensive physical methods and chemically hazardous



**Figure 1** An overview of the administration routes for selenium nanomedicines in ocular diseases discussed in this review, including topical application, intravitreal injection, and systemic administration. Created in BioRender.

**Abbreviations:** GRX, glutaredoxin; GSH, glutathione;  $H_2Se$ , hydrogen selenide; ILM, internal limiting membrane; RPE, retinal pigment epithelium; Sec, selenocysteine; SPS2, selenophosphate synthetase 2; TRX, thioredoxin; TXNRD, thioredoxin reductase gene.

routes, combining operational sustainability, cost-effectiveness, and intrinsic biocompatibility. Consequently, biosynthetic SeNPs are positioned as highly suitable for pharmaceutical and therapeutic applications.<sup>28,29,87</sup>

## Therapeutic Mechanisms and Applications of Selenium Nanomedicines in Ocular Diseases

The therapeutic significance of elemental Se in ophthalmology is well-established; however, the exploration of Se-based nanomedicines is a more recent development, with most advancements occurring within the past five years. This review provides a timely synthesis of these developments, focusing on innovative platforms such as zero-valent SeNPs, Se-based composite nanomaterials (e.g., TPGS-SeNPs, Ciprofloxacin-SeNPs, LBP-SeNPs, CSA@Se-PEG-PPG micelles, and

Porous Se@SiO<sub>2</sub>), and metal selenides (e.g., Cu<sub>2-x</sub>Se nanoparticles, CdSe/ZnS QDs). These nanoplateforms facilitate precise ocular therapy by leveraging the inherent bioactivity of Se, enabling targeted and stimulus-responsive drug delivery, and promoting synergistic therapeutic effects. Certain metal selenides further contribute through physical energy conversion. As summarized in Table 1, the current evidence for these benefits comes predominantly from preclinical studies, with a single Phase I clinical trial reported to date. Within these studies, the nanoplateforms have demonstrated a wide range of beneficial functions, including antioxidative, anti-inflammatory, anti-angiogenic, antimicrobial, barrier-repairing, and neuroprotective effects, alongside their utility as drug carriers (Figure 2).

## Retinal Neovascularization

Retinal neovascular diseases, including proliferative DR, RVO, and retinopathy of prematurity (ROP), are leading causes of global blindness. Current standard treatments such as laser photocoagulation, anti-VEGF therapy, and vitrectomy, are often limited by complications including retinal detachment, vision loss, cataract, and endophthalmitis.<sup>28,94</sup> Given that SeNPs have demonstrated significant anti-angiogenic effects in oncology by inducing apoptosis and cell cycle arrest,<sup>95,96</sup> their application has been logically extended to retinal neovascularization.

For instance, Nie et al developed biosynthetic spherical SeNPs (15–50 nm) using lyophilized grape extract. These nanoparticles exhibited potent, dose-dependent anti-angiogenic effects in human umbilical vein endothelial cells (HUVECs), suppressing proliferation, migration, and tube formation without apparent cytotoxicity. In a murine oxygen-induced retinopathy (OIR) model, intravitreal injection of SeNPs attenuated pathological angiogenesis by suppressing endothelial cell proliferation. However, they were also found to disrupt normal angiogenic processes in a retinal vascular development model, raising important safety considerations regarding their potential impact on physiological retinal development or repair. Mechanistically, SeNPs inhibited the PI3K-AKT pathway, leading to the upregulation of p21 and downregulation of key cell cycle regulators (CDK2, Cyclin A1, MCM5/7), thereby inducing G1 phase cell cycle arrest. Unlike sodium selenite, which lacked efficacy at non-toxic doses, SeNPs demonstrated a superior therapeutic profile. Therefore, while SeNPs represent a promising novel anti-angiogenic agent, their non-selective mechanism necessitates the development of targeted delivery strategies to minimize off-target effects on healthy vasculature (Figure 3).<sup>28</sup> Future research directions must focus on engineering next-generation SeNPs with enhanced targeting capabilities to discriminate between pathological and physiological angiogenesis, thereby improving therapeutic specificity and safety for a broader range of ocular vascular disorders.

## Diabetic Retinopathy

DR, a major microvascular complication of diabetes and a leading cause of global vision loss, affected over 103 million individuals worldwide by 2020. Its progression, driven by hyperglycemia, involves interconnected pathways of oxidative stress, chronic inflammation, advanced glycation end products (AGEs) accumulation, and VEGF upregulation. The current standard of care for proliferative DR (PDR) and diabetic macular edema (DME) includes laser photocoagulation, intravitreal anti-VEGF or corticosteroid injections, and vitreoretinal surgery.<sup>97</sup> Studies indicate that SeNPs can manage diabetes by enhancing insulin delivery, providing antioxidant activity, and modulating inflammatory cytokines, thereby improving glycemic control, lipid metabolism, and antioxidant capacity.<sup>98,99</sup>

Khashaba et al demonstrated the superior efficacy of chemically synthesized spherical SeNPs (20–25 nm) over elemental Se in a rat model of streptozotocin (STZ)-induced DR. The therapeutic action of SeNPs is multifaceted: they significantly reduced blood glucose with a faster onset than elemental Se (by week 3), mitigated oxidative stress by enhancing total antioxidant capacity (TAC) and reducing malondialdehyde (MDA) levels, and inhibited the TLR4/NF-κB signaling pathway to attenuate pro-inflammatory cytokine release. Furthermore, SeNPs downregulated VEGF expression, reducing pathological neovascularization, and markedly improved retinal architecture. This architectural improvement was associated with the restoration of connexin 43 (Cx43) expression and a downregulation of glial fibrillary acidic protein (GFAP), thereby facilitating intercellular communication and reducing excessive glial cell activation (Figure 4).<sup>27</sup> These findings underscore the potential of SeNPs as a novel therapeutic agent for DR. Future research should validate these signaling pathways using genetic methodologies and assess the long-term impacts of SeNPs on retinal tissue.

**Table I** Summary of Selenium Nanomedicines in Different Ocular Diseases

| Nanoformulations (Size)                                                    | Diseases                   | Experimental Models                                                                                                    | Administrations        | Key Outcomes                                                                                                                                                                                                                               | Mechanism                                                                                                                                     | References |
|----------------------------------------------------------------------------|----------------------------|------------------------------------------------------------------------------------------------------------------------|------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|------------|
| SeNPs (15–50 nm)                                                           | Retinal neovascularization | <ul style="list-style-type: none"> <li>HUVECs</li> <li>OIR mice</li> <li>Retinal vascular development model</li> </ul> | Intravitreal injection | <ul style="list-style-type: none"> <li>Inhibit vascular endothelial cell functions in vivo and in vitro</li> </ul>                                                                                                                         | <ul style="list-style-type: none"> <li>Regulate PI3K-AKT-p21 axis</li> <li>G1/S cell cycle arrest</li> </ul>                                  | [28]       |
| SeNPs (20–25 nm)                                                           | DR                         | STZ-induced DR rat                                                                                                     | Oral                   | <ul style="list-style-type: none"> <li>Preserve retinal structure</li> <li>Reduce oxidative stress and inflammation</li> </ul>                                                                                                             | <ul style="list-style-type: none"> <li>↑ TAC, ↓ MDA</li> <li>↓ TLR4/NF-κB</li> <li>↓ VEGF</li> <li>↑ Connexin 43</li> <li>↓ GFAP</li> </ul>   | [27]       |
| SeNPs (30–60 nm)                                                           | Retinal hypoxia            | Hypoxia-induced ARPE-19 cells                                                                                          | Incubation             | <ul style="list-style-type: none"> <li>Decrease cell death</li> <li>Inhibit mitochondrial membrane depolarization</li> <li>Reduce ROS generation and inflammation</li> </ul>                                                               | <ul style="list-style-type: none"> <li>↓ TRPM2 currents and calcium influx</li> <li>↓ PARP-1</li> <li>↓ TNF-α and IL-1β</li> </ul>            | [88]       |
| TPGS-SeNPs (44 ± 3 nm)                                                     | Cataract                   | H <sub>2</sub> O <sub>2</sub> -induced HLECs                                                                           | Incubation             | <ul style="list-style-type: none"> <li>Scavenge free radicals</li> <li>Modulate antioxidant enzyme activities</li> </ul>                                                                                                                   | <ul style="list-style-type: none"> <li>↑ GPX and TrxR activity</li> </ul>                                                                     | [90]       |
| LBP-SeNPs (150–200 nm)                                                     | Cataract                   | UVB-induced HLECs                                                                                                      | Incubation             | <ul style="list-style-type: none"> <li>Enhance cell proliferation</li> <li>Attenuate oxidative damage</li> </ul>                                                                                                                           | <ul style="list-style-type: none"> <li>Combined antioxidant effects of LBP and SeNPs</li> </ul>                                               | [89]       |
| SeNPs–Cipro (SeNPs: 78–190 nm)                                             | Acanthamoeba keratitis     | Acanthamoeba castellanii                                                                                               | Incubation             | <ul style="list-style-type: none"> <li>Enhance anti-protozoal efficacy</li> <li>Inhibit cyst formation</li> <li>Low cytotoxicity</li> </ul>                                                                                                | <ul style="list-style-type: none"> <li>Disrupt cell membrane</li> <li>↓ enzyme (protease, β-galactosidase)</li> </ul>                         | [29]       |
| Cu <sub>2-x</sub> Se NPs@AFI27 hydrogel (Cu <sub>2-x</sub> Se NPs ~2.8 nm) | DED                        | <ul style="list-style-type: none"> <li>HCECs</li> <li>Dry eye murine model</li> </ul>                                  | Eye drops              | <ul style="list-style-type: none"> <li>Scavenge ROS</li> <li>Promote corneal epithelial repair</li> <li>Restore tear secretion and goblet cells density</li> </ul>                                                                         | <ul style="list-style-type: none"> <li>Exhibit SOD/GPX-like activity</li> <li>↑ NRF2 pathway</li> <li>↓ p38 MAPK signaling</li> </ul>         | [91]       |
| CSA@Se-PEG-PPG micelles (42–46 nm)                                         | DED                        | <ul style="list-style-type: none"> <li>HCECs</li> <li>Dry eye murine model</li> </ul>                                  | Eye drops              | <ul style="list-style-type: none"> <li>Enhance corneal penetration and cellular uptake</li> <li>Improve corneal repair and tear production</li> <li>Preserve goblet cell density</li> <li>Reduce apoptosis and oxidative stress</li> </ul> | <ul style="list-style-type: none"> <li>ROS-responsive drug release</li> <li>Synergistic antioxidant and anti-inflammatory activity</li> </ul> | [76]       |

|                                                |    |                                                                                           |                                        |                                                                                                                                                                                 |                                                                                                                                                                              |      |
|------------------------------------------------|----|-------------------------------------------------------------------------------------------|----------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|
| Porous Se@SiO <sub>2</sub> nanospheres (55 nm) | DR | <ul style="list-style-type: none"> <li>• Diabetic db/db mice</li> <li>• HRMECs</li> </ul> | Intravitreal injection                 | <ul style="list-style-type: none"> <li>• Alleviate retinal vasculopathy</li> <li>• Suppress lipid peroxidation and inflammation</li> <li>• Restore redox homeostasis</li> </ul> | <ul style="list-style-type: none"> <li>• ↓ MDA,</li> <li>• ↓ TNF-<math>\alpha</math>, IFN-<math>\gamma</math>, IL-1<math>\beta</math></li> <li>• ↑ GPX4, GSH/GSSG</li> </ul> | [92] |
| CdSe/ZnS QDs ( $\leq 6.5$ nm)                  | RP | RP patients in a Phase I trial (n=20) (Clinical Trial: NCT04008771)                       | Intravitreal injection (0.2/2 $\mu$ M) | <ul style="list-style-type: none"> <li>• No serious adverse events</li> <li>• BCVA improvement</li> </ul>                                                                       | <ul style="list-style-type: none"> <li>• Photoelectric stimulation of residual retinal neurons</li> </ul>                                                                    | [93] |

**Notes** ↑ indicates increase or upregulation; ↓ indicates decrease or downregulation.

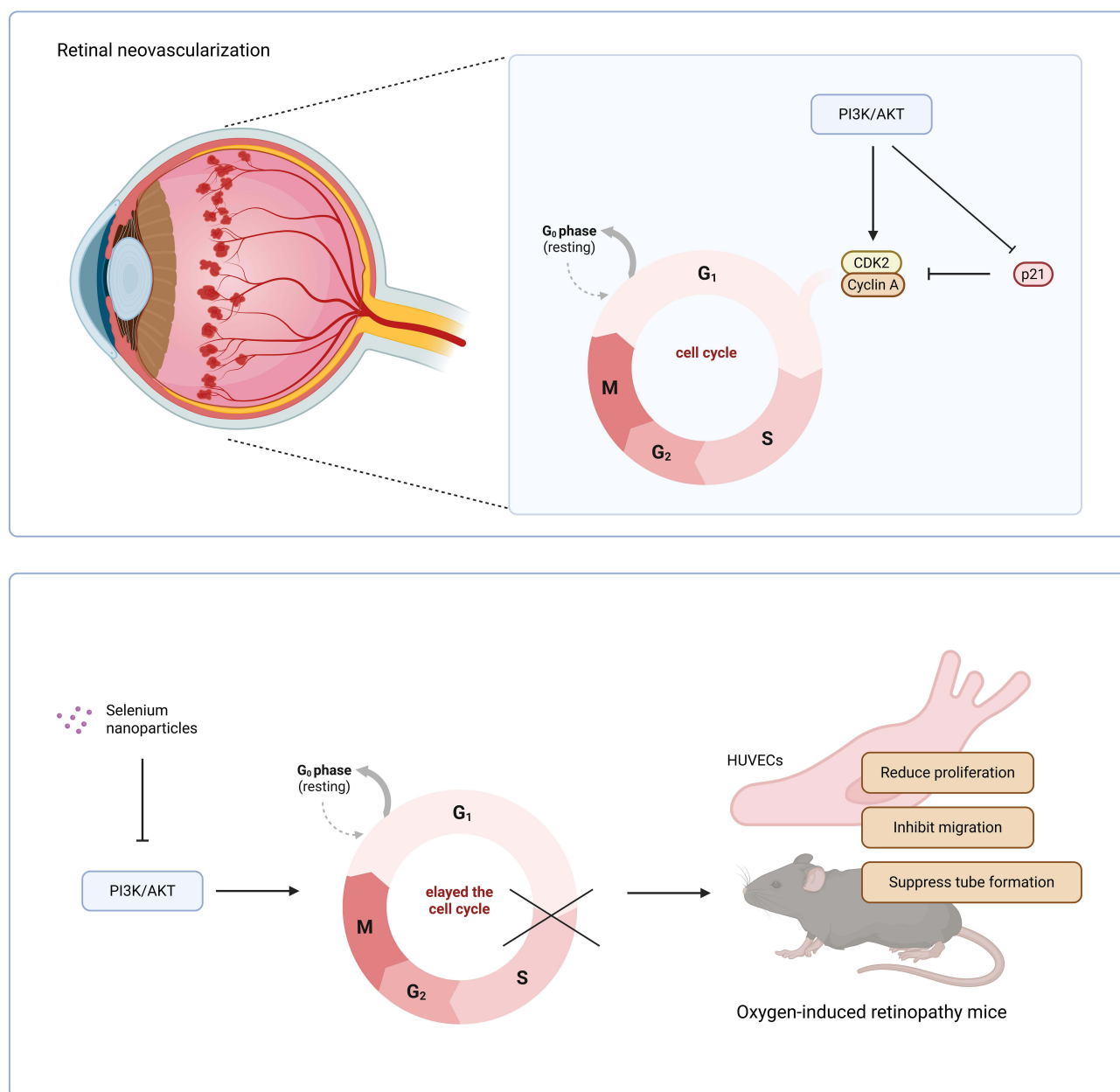
**Abbreviations:** ARPE-19, retinal pigment epithelial cell line; BCVA, best-corrected visual acuity; Cipro, ciprofloxacin; CSA, cyclosporine A; DED, Dry eye disease; DR, Diabetic retinopathy; GFAP, glial fibrillary acidic protein; GPX, glutathione peroxidase; GSH/GSSG, reduced/oxidized glutathione; HCECs, human corneal epithelial cells; HLECs, human lens epithelial cells; HRMECs, human retinal microvascular endothelial cells; HUVECs, human umbilical vein endothelial cells; IFN- $\gamma$ , interferon-gamma; IL-1 $\beta$ , interleukin-1 beta; LBP, Lycium barbarum polysaccharide; MAPK, mitogen-activated protein kinase; MDA, malondialdehyde; NRF2, nuclear factor erythroid 2-related factor 2; OIR, oxygen-induced retinopathy; PARP-I, poly(ADP-ribose) polymerase-I; PEG-PPG, polyethylene glycol-polypropylene glycol; PI3K-AKT, phosphoinositide 3-kinase–protein kinase B; QDs, quantum dots; RP, Retinitis pigmentosa; ROS, reactive oxygen species; SeNPs, selenium nanoparticles; SiO<sub>2</sub>, silica/silicon dioxide; SOD, superoxide dismutase; STZ, streptozotocin; TAC, total antioxidant capacity; TLR4/NF- $\kappa$ B, Toll-like receptor 4/Nuclear factor kappa B; TNF- $\alpha$ , tumor necrosis factor-alpha; TPGS, D- $\alpha$ -tocopheryl polyethylene glycol succinate; TRPM2, transient receptor potential melastatin 2; TrxR, thioredoxin reductase; VEGF, vascular endothelial growth factor.



**Figure 2** Therapeutic Mechanisms and Applications of selenium nanomedicines in different ocular diseases. Created in BioRender.

**Abbreviations:** CSA, cyclosporine A;  $\text{Cu}_{2-x}\text{Se}$  NPs, copper-selenide nanoparticles; DED, dry eye disease; DR, diabetic retinopathy; LBP, Lycium barbarum polysaccharide; NPs, nanoparticles; PEG, polyethylene glycol; PPG, polypropylene glycol; RP, retinitis pigmentosa; ROS, reactive oxygen species; SeNPs, selenium nanoparticles; TPGS, D- $\alpha$ -tocopheryl polyethylene glycol succinate.

Niu et al synthesized porous  $\text{Se}@\text{SiO}_2$  nanosphere (~55 nm) featuring a Se core within a porous silica shell. Post-synthesis etching optimized pore structure for controlled Se release, enhancing bioavailability while minimizing toxicity.<sup>100</sup> In diabetic db/db mice, a single intravitreal injection of these nanospheres significantly alleviated retinal vasculopathy. The treatment suppressed retinal lipid peroxidation (reduced MDA), attenuated inflammation, as evidenced by decreased levels of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interferon- $\gamma$  (IFN- $\gamma$ ), and interleukin-1 $\beta$  (IL-1 $\beta$ ), and restored redox homeostasis by upregulating GPX4 and increasing the reduced/oxidized GSH (GSH/GSSG) ratio. These effects collectively enhanced blood-retinal barrier integrity by upregulating tight junction proteins and reducing acellular capillaries. Crucially, GPX4 was validated as the key therapeutic target in high glucose-cultured human retinal



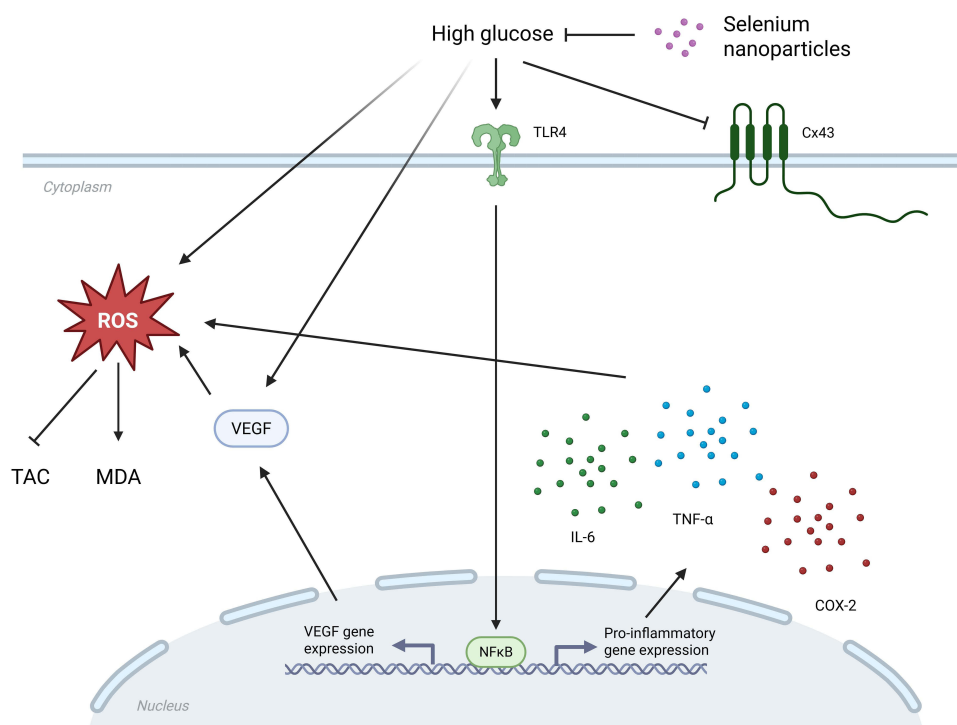
**Figure 3** SeNPs attenuate pathological angiogenesis by suppressing endothelial cell proliferation, which is achieved by cell cycle arrest via targeting the PI3K/AKT/p21 axis. Created in BioRender.

**Abbreviations:** AKT, Protein Kinase B; CDK2, Cyclin-Dependent Kinase 2; HUVECs, Human Umbilical Vein Endothelial Cells; M, Mitosis phase; p21, Cyclin-dependent Kinase Inhibitor 1A; PI3K, Phosphatidylinositol 3-Kinase.

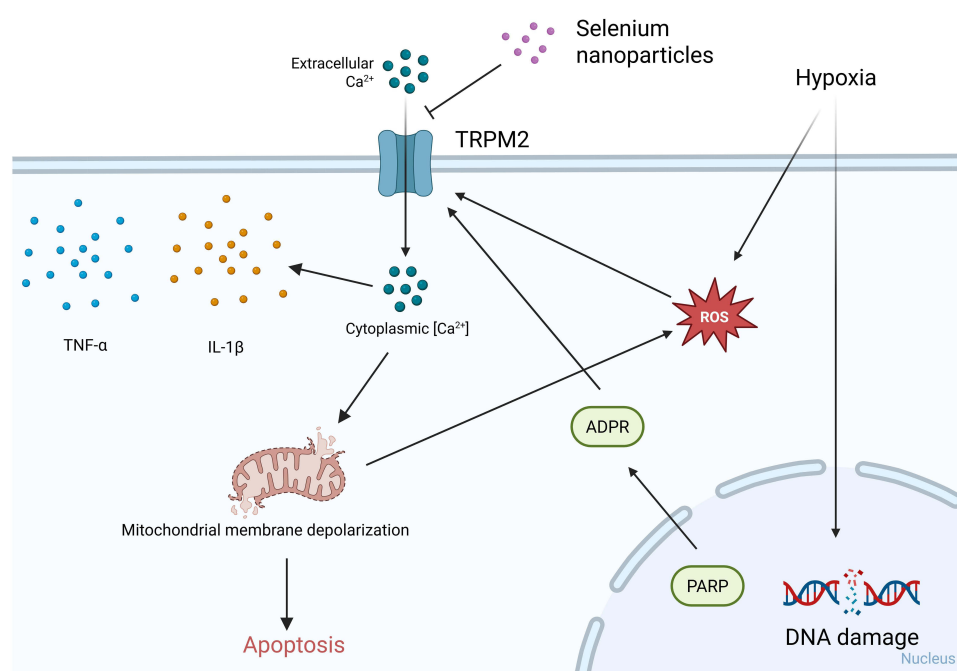
microvascular endothelial cells (HRMECs).<sup>92</sup> This controlled-release strategy presents a novel, non-anti-VEGF therapeutic avenue for treatment-insensitive patients.

## Retinal Hypoxia

Retinal hypoxia is a pivotal driver in the pathogenesis of numerous retinal disorders, including glaucoma, DR, and RVO. The ensuing overproduction of VEGF leads to pathological neovascularization, breakdown of the blood-retinal barrier, and inflammatory damage to neurons and glial cells, ultimately resulting in retinal function loss. Current treatments encompass anti-VEGF therapy, hypoxia-inducible factor (HIF) inhibitors, and strategies to improve oxygen supply and



**Figure 4** The therapeutic action of SeNPs is multifaceted, involving the inhibition of multiple pathways induced by hyperglycemia. Created in BioRender.  
**Abbreviations:** COX2: Cyclooxygenase-2; Cx43, Connexin 43; IL-6, Interleukin-6; MDA, Malondialdehyde; NFκB, Nuclear Factor-κB; ROS, Reactive Oxygen Species; TAC, Total Antioxidant Capacity; TLR4, Toll-like Receptor 4; TNF-α, Tumor Necrosis Factor-α; VEGF, Vascular Endothelial Growth Factor.



**Figure 5** PEGylated SeNPs confer protection against hypoxic retinal injury by suppressing TRPM2 current density. Created in BioRender.  
**Abbreviations:** ADPR, adenosine diphosphate ribose; Ca<sup>2+</sup>, calcium ion; IL-1β, interleukin-1β; PARP, poly(ADP-ribose) polymerase; ROS, reactive oxygen species; TNF-α, tumor necrosis factor-α; TRPM2, transient receptor potential melastatin 2.

provide neuroprotection.<sup>101</sup> Given the confirmed roles of SeNPs in antioxidant, anti-inflammatory, and mitochondrial protection in cerebral hypoxia,<sup>102</sup> their potential utility in retinal hypoxic environments is substantial.

A mechanistic study by Ozkaya D et al demonstrated that in retinal pigment epithelial (ARPE-19) cells, hypoxia triggers DNA damage, activating poly (ADP-ribose) polymerase-1 (PARP-1) to generate adenosine diphosphate-ribose (ADPR). ADPR, together with ROS, co-activates the transient receptor potential melastatin 2 (TRPM2) channel, provoking substantial  $\text{Ca}^{2+}$  influx. This cascade leads to mitochondrial membrane depolarization, excessive ROS production, and release of inflammatory cytokines (TNF- $\alpha$ , IL-1 $\beta$ ), ultimately causing apoptotic cell death. Their findings indicate that PEGylated SeNPs confer protection by suppressing TRPM2 current density, downregulating PARP-1 and TRPM2 expression, and thereby mitigating these pathological markers, identifying TRPM2 blockade as a potential therapeutic strategy for hypoxic retinal injury (Figure 5).<sup>88</sup> This study, however, is confined to an in vitro model, necessitating further in vivo validation. Moreover, the precise molecular mechanism, including potential direct interaction with TRPM2, remains elusive, warranting future research into combinatory therapies of SeNPs with other antioxidants.

## Cataract

Oxidative stress serves as a pivotal factor in cataract development, as the ocular lens is prone to oxidative damage from long-lived proteins, constant light exposure, and waning antioxidant capacity with age. This leads to ROS accumulation, protein oxidation, aggregation, and lens opacity.<sup>90</sup>

Zhong et al demonstrated that SeNPs loaded with lycium barbarum polysaccharide (LBP-SeNPs, 150–200 nm) significantly protect human lens epithelial cells (HLECs) from UVB-induced damage. Within an optimal concentration range (0.5–4  $\mu\text{mol/L}$ ), LBP-SeNPs promoted cell proliferation with low cytotoxicity. The most effective formulation (0.5  $\mu\text{mol/L}$ , 2.0 mg/mL LBP-SeNPs) achieved a proliferation rate of 128.80%, whereas higher concentrations induced apoptosis.<sup>89</sup> The protective effect is attributed to the combined antioxidant capacity of LBP and the enhanced cellular uptake provided by the nano-Se platform, identifying LBP-SeNPs as a promising nanotherapeutic strategy for cataract prevention that warrants in vivo validation.

In a separate study, Al-Bassam et al synthesized stable, spherical SeNPs coated with D- $\alpha$ -tocopheryl polyethylene glycol succinate (TPGS-SeNPs, ~44 nm). These nanoparticles exhibited potent free radical scavenging activity in vitro. A key finding was that at a low, biocompatible concentration ( $\leq 0.4 \mu\text{g/mL}$ ), TPGS-SeNPs selectively enhanced the activity of key endogenous antioxidant enzymes, activating GPX more effectively than an equivalent dose of selenomethionine and dose-dependently increasing TrxR activity. At this concentration, they protected against  $\text{H}_2\text{O}_2$ -induced cell death, whereas higher concentrations led to reduced adenosine triphosphate (ATP) production and mitochondrial dysfunction, indicating potential toxicity.<sup>90</sup> Further in vivo studies are warranted to evaluate ocular penetration and therapeutic efficacy.

## Ocular Infections

SeNPs demonstrate broad-spectrum antimicrobial activity through synergistic mechanisms, primarily via ROS-induced oxidative damage to microbial lipids, proteins, and DNA. In bacteria and fungi, they compromise membrane and cell wall integrity, causing content leakage and metabolic disruption. Against viruses, SeNPs bind to key structural proteins such as viral spikes to prevent host cell infection, while also potentially enhancing immune-mediated antiviral response.<sup>103</sup> To date, direct experimental evidence from ocular-specific viral infection models remains lacking in this context.

This potential is exemplified in the treatment of *Acanthamoeba* keratitis, a vision-threatening corneal infection. The disease is caused by the protozoan *Acanthamoeba*, which has a life cycle involving both active trophozoites and dormant cysts. To address the severe side effects of prolonged ciprofloxacin (Cipro) use, Nikam et al conjugated the antibiotic with SeNPs (SeNPs-Cipro). The conjugate exhibited potent synergistic anti-amoebic activity, reducing the  $\text{LC}_{50}$  by 33.43%, suppressing cyst formation, and completely blocking excystation. These effects were mediated through the inhibition of  $\beta$ -galactosidase and protease, coupled with membrane leakage that led to trophozoite death, all with minimal cytotoxicity.<sup>29</sup> This study highlights the role of SeNPs as drug delivery carriers that lower effective antibiotic dosages

and associated toxicities. These findings support further preclinical study of SeNPs-Cipro and future testing of SeNPs with other antibiotics to combat resistance.

## Dry Eye Disease

The majority of DED is driven by oxidative stress and excessive inflammation, resulting in tear deficiency and increased tear evaporation. Conventional eye drops are limited by their brief precorneal residence time, necessitating high dosages and frequent application.<sup>104</sup> Nanomaterial-based strategies present a promising alternative by facilitating prolonged residence and multitargeted therapy.

Ou et al developed an aldehyde-functionalized F127 hydrogel (AF127) loaded with ultrasmall (~2.8 nm) antioxidant copper-selenide nanoparticles ( $\text{Cu}_{2-x}\text{Se}$  NPs). These nanoparticles served as dual nanozymes, mimicking both SOD and GPX to effectively scavenge ROS. In human corneal epithelial cells (HCECs), they alleviated oxidative damage, suppressed apoptosis, and reduced inflammation by activating the nuclear factor erythroid 2-related factor 2 (NRF2) pathway and inhibiting p38 mitogen-activated protein kinase (MAPK) signaling. In a murine DED model, the formulation repaired the corneal epithelium, restored conjunctival goblet cells, and enhanced tear secretion. The AF127 hydrogel adhered strongly to the ocular surface via Schiff base bonding, improving retention, with no notable toxicity observed.<sup>91</sup> This work pioneers the ophthalmic use of  $\text{Cu}_{2-x}\text{Se}$  NPs, offering a multifunctional, efficient, and safe nanotherapeutic strategy for ROS-related ocular diseases.

To address the poor solubility and low corneal permeability of cyclosporine A (CSA), Yang et al developed an innovative ROS-responsive nanocarrier. The system is based on a Se-containing copolymer, Se-PEG-PPG, which self-assembles into sub-50 nm micelles ( $\text{CSA}@\text{Se-PEG-PPG}$ ) with a neutral surface charge. This design enables efficient encapsulation of highly hydrophobic immunosuppressive CSA and provides inherent antioxidative capacity for dual-target therapy. The copolymer demonstrated good biocompatibility, rescued  $\text{H}_2\text{O}_2$ -induced oxidative stress in HCECs, and facilitated outstanding cellular uptake. Both ex-vivo and in-vivo studies confirmed high corneal permeability and the formulation outperformed commercial CSA eye drops in restoring corneal integrity, promoting tear secretion, and preserving goblet cell density.<sup>76</sup> This work presents an integrated Se nanomedicine strategy that combines enhanced ocular drug delivery with inherent antioxidant and anti-inflammatory actions.

## Retinitis Pigmentosa

The superior optical properties of QDs enable high-resolution imaging and targeted therapy via photoelectric conversion.<sup>105</sup> Specifically, CdSe/ZnS QDs have demonstrated therapeutic efficacy for retinal degeneration, enhancing electroretinogram responses and preserving retinal cytoarchitecture in RCS rats.<sup>106</sup>

A first-in-human Phase 1 safety study (NCT04008771) of intravitreally injected CdSe/ZnS QDs in 20 retinitis pigmentosa (RP) patients demonstrated a favorable tolerability profile. The core cadmium selenide is isolated by a robust dual-layer encapsulation, specifically, a ZnS shell and a hydrophilic dipeptide coating, which effectively mitigates biosafety concerns. Indeed, no adverse events were attributed to the QDs in the study. Notably, mean best corrected visual acuity (BCVA) improved in patients with severe RP, supporting the feasibility of larger clinical trials. Owing to their intraretinal migration and retention, QDs enable repeatable dosing.<sup>93</sup> Consequently, they present a promising therapeutic profile compared to retinal implants and gene therapy, characterized by minimal invasiveness, applicability across genetic subtypes, and fully titratable treatment regimens.

## Challenges and Future Prospects

The advent of nanomedicine has revolutionized ophthalmology by overcoming the physiological barriers that limit conventional therapies. Approved agents, such as liposomal verteporfin (Visudyne<sup>®</sup>) for wet AMD and sustained-release dexamethasone implants (Ozurdex<sup>®</sup>) for macular edema, demonstrate how nanocarriers enhance bioavailability, enable controlled and targeted delivery.<sup>6</sup> Building upon this foundation and the established role of elemental Se in ophthalmology, Se nanomedicine has emerged as a highly promising therapeutic platform. Its potential is underpinned by multiple mechanisms validated in preclinical and clinical studies: (1) GPX-mimicking antioxidant and anti-inflammatory bioactivities; (2) enhanced ocular bioavailability through nanoengineering such as size optimization and surface charge

modulation; (3) stimuli-responsive drug release; (4) versatile combinatorial therapy capabilities; and (5) integrated theranostic potential.

Despite robust preclinical evidence, the clinical translation of Se nanomedicines faces substantial challenges. A primary hurdle is the anatomical and physiological discrepancies between animal models and humans, which complicates the direct extrapolation of experimental data. Furthermore, the biotransformation mechanisms of these nanomedicines within ocular tissues remain poorly characterized, limiting a mechanistic understanding of their cellular interactions and long-term effects.<sup>5</sup> The biosafety and efficacy of these nanoparticles are fundamentally governed by their physicochemical properties, such as size, morphology, surface charge, and composition, which dictate their biological interactions, protein corona formation, biodistribution, and potential for aggregation-induced capillary occlusion or immune activation.<sup>107</sup> To bridge this translational gap, establishing a comprehensive preclinical biosafety profile is imperative. This requires systematic evaluation of degradation kinetics, long-term biodistribution, PK/pharmacodynamics (PK/PD), ideally aligned with the ADME-Tox (absorption, distribution, metabolism, excretion, and toxicity) framework used for conventional pharmaceuticals.<sup>105</sup>

Advancing the field further necessitates a dual focus on manufacturing and regulation. There is a pressing need to develop scalable, green synthesis methods for biogenic SeNPs that ensure high bio-efficacy, low toxicity, and structural stability. Simultaneously, critical regulatory gaps must be addressed, particularly the classification uncertainties arising from insufficient long-term biosafety data, which currently hinder standardized manufacturing and clinical approval.<sup>20,26</sup>

Se nanomedicines are advancing ophthalmic therapy toward intelligent and precision medicine through several pathology-driven strategies. A key development is theranostic SeNP platforms, which integrate contrast agents for non invasive, real-time visualization of drug distribution. This is particularly valuable for posterior segment diseases like choroidal melanoma and DME, as it provides critical pharmacokinetic data for treatment monitoring and dosage optimization. Furthermore, compartment-specific targeting is achieved through the strategic surface engineering of SeNPs. For anterior segment applications such as bacterial keratitis and DED, mucoadhesive coatings enhance corneal residence time. Conversely, for posterior segment disorders including neovascular AMD and DR, the conjugation of active targeting ligands facilitates specific cellular uptake. Another significant strategy involves pathology-responsive SeNPs systems that leverage Se's intrinsic redox activity for spatiotemporally controlled drug release. These systems can be engineered to release their payload in response to pathological stimuli, such as elevated intraocular ROS or inflammation-associated acidic pH, enabling spatiotemporally precise intervention in conditions like DR, immune-mediated uveitis and ocular tumors.<sup>108</sup> Given these versatile mechanisms, SeNPs demonstrate clear potential for broader application in ocular diseases. However, it should be noted that direct preclinical evidence of their efficacy in specific pathologies, including DME, bacterial keratitis, uveitis, and ocular tumors, remains unreported. Nonetheless, the fundamental pharmacological properties of SeNPs indicate promising directions for future research across a wider spectrum of ocular conditions. Looking forward, the integration of artificial intelligence (AI) and machine learning is revolutionizing this field. These tools facilitate the rational design of nanodrugs, predict their efficacy and toxicity, and enable personalized therapeutic strategies, thereby streamlining the entire development pipeline for intelligent nanomedicines like SeNPs.<sup>109</sup>

## Conclusions

In conclusion, Se nanomedicines represent a promising paradigm in ocular therapeutics by unifying targeted drug delivery, intrinsic bioactivity, and diagnostic capabilities into a single platform. Their multifunctionality enables therapeutic potential across a spectrum of ocular diseases, as demonstrated by their potent antioxidative, anti-inflammatory, anti-angiogenic, antimicrobial, barrier-repairing, and neuroprotective functions. A key advantage lies in their engineerability, allowing for precise drug delivery to specific ocular structures while concurrently functioning as imaging agents for therapeutic monitoring. Although current research efforts are largely centered on preclinical development, early-phase clinical trials have initiated the exploration of their translational feasibility.

However, the clinical translation of these nanomaterials faces several critical hurdles, including dose-dependent toxicity profiles, interspecies disparities between animal models and human physiology, and the lack of standardized, scalable manufacturing protocols. Future research must therefore focus on optimizing material properties through

computational design, exploring synergistic combination therapies, and conducting rigorous, long-term safety studies. By systematically addressing these challenges, Se nanomedicines hold strong potential to evolve into effective clinical treatments for vision-threatening diseases, offering novel solutions to unmet needs in ocular therapeutics.

## Abbreviations

ADME, absorption, distribution, metabolism, and excretion; ADPR, adenosine diphosphate-ribose; AGEs, advanced glycation end products; AI, artificial intelligence; AMD, age-related macular degeneration; ARC, age-related cataract; ATP, adenosine triphosphate; BCVA, best corrected visual acuity; CAT, catalase; Cx43, connexin 43; Cipro, ciprofloxacin; CSA, cyclosporine A; Cu<sub>2-x</sub>Se NPs, copper-selenide nanoparticles; DED, dry eye disease; DIO, iodothyronine deiodinases; DME, diabetic macular edema; DR, diabetic retinopathy; GFAP, glial fibrillary acidic protein; GO, Graves' Orbitopathy; GPX, glutathione peroxidase; GRX, Glutaredoxin; GSH, glutathione; GST, glutathione S-transferase; GSSG, glutathione disulfide; H<sub>2</sub>Se, hydrogen selenide; HCECs, human corneal epithelial cells; HIF, hypoxia-inducible factor; HRMECs, human retinal microvascular endothelial cells; HLECs, human lens epithelial cells; HUVECs, human umbilical vein endothelial cells; IFN- $\gamma$ , interferon- $\gamma$ ; IL-1 $\beta$ , interleukin-1 $\beta$ ; LBP, lycium barbarum polysaccharide; LD<sub>50</sub>, median lethal dose; MAPK, mitogen-activated protein kinase; MDA, malondialdehyde; MPS, mononuclear phagocyte system; NRF2, nuclear factor erythroid 2-related factor 2; OIR, oxygen-induced retinopathy; PARP-1, poly (ADP-ribose) polymerase-1; PDR, proliferative diabetic retinopathy; PD, pharmacodynamics; PEG, polyethylene glycol; PK, pharmacokinetics; PLA, pulsed laser ablation; QDs, quantum dots; ROP, retinopathy of prematurity; ROS, reactive oxygen species; RPE, retinal pigment epithelium; RP, retinitis pigmentosa; RVO, retinal vascular occlusion; SBP1, Se-binding protein 1; SCLY, selenocysteine lyase; Se, selenium; Sec, selenocysteine; SeNPs, selenium nanoparticles; SOD, superoxide dismutase; SPS2, selenophosphate synthetase 2; STZ, streptozotocin; TAC, total antioxidant capacity; theranostic, therapeutic and diagnostic; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ ; TPGS, D- $\alpha$ -tocopheryl polyethylene glycol succinate; TRAb, thyrotropin receptor antibodies; TRPM2, transient receptor potential melastatin 2; Trx, thioredoxin; TrxR, thioredoxin reductase; TXNRD, thioredoxin reductase gene; VEGF, vascular endothelial growth factor; Vit E, vitamin E;  $\gamma$ -GCS,  $\gamma$ -glutamylcysteine synthetase.

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## Disclosure

The authors report no conflicts of interest in this work.

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