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Biomedical functions and applications of nanomaterials in tumor diagnosis and treatment: perspectives from ophthalmic oncology

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Highlights:

- This review highlights how multifunctional polymeric nanocarriers enhance drug stability, tumor penetration, and release.
- This review showcases theranostic nanomedicine for integrated diagnosis, therapy, and monitoring of ocular tumors.
- The review discusses emerging strategies: AI-assisted design, combinatorial therapies, and personalized nanomedicine.

Abstract: Nanoparticle-based therapies have emerged as a promising approach in oncology, offering enhanced drug delivery, precise targeting, and improved imaging capabilities. This review examines the pivotal role of nanoparticles in therapy from the perspective of ocular tumors, with a particular emphasis on their biomedical functions and applications, while also addressing the challenges currently faced in this field. This review also outlines future directions in the field, encompassing advanced targeting strategies, combination therapy regimens, AI-driven platforms, and personalized nanomedicine, aimed at providing advanced perspectives on nanoparticles in ophthalmic oncology.

Keywords: nanoparticle; ophthalmology tumor; biomedical functions and applications

1. Introduction

Nowadays, nanoparticles (typically 1–100 nm) have become star tools due to their tunable size, surface chemistry, and ability to be functionalized for precise drug delivery [1–4]. Their use is similarly significant in ophthalmology, where they help overcome the challenges of the blood-retina barrier, enabling targeted drug delivery in ocular tumors [5–7]. Additionally, laser-activated multifunctional nanoparticles provide precise spatiotemporal control over drug release, offering improved treatment outcomes for retinoblastoma [8,9]. These advancements in nanoparticle design highlight their potential to enhance the precision, efficacy, and safety of ocular tumor therapies, making them a promising platform for future treatments.

However, their clinical translation is hindered by concerns over ocular toxicity, immune reactions, and prolonged clearance. To overcome these limitations, researchers have shifted attention from carrier design to functional mechanisms. They exploit endogenous biology or external stimuli, such as label-free attenuated total reflection fourier transform infrared spectroscopy (ATR-FTIR) monitoring of retinoblastoma response [2] or ultrasound-triggered localized therapy [3]. Meanwhile, Polymeric nanoparticles, such as glycol chitosan, have been utilized to deliver dual-targeted siRNAs against VEGF and Bcl-2, effectively suppressing tumor growth and enhancing therapeutic outcomes [10]. Furthermore, tumor-homing Tumor necrosis factor-related apoptosis inducing ligand (TRAIL) sensitizers conjugated with nanoparticles improve drug delivery and therapy efficacy, addressing challenges such as drug resistance and short circulation times [11]. These innovations underscore the potential of nanotechnology to integrate therapeutic, diagnostic, and theranostic functions in the management of ocular tumors.

Despite its achievements, nanoparticle-based therapies for ophthalmic tumors still face significant challenges, including ocular toxicity, where prolonged exposure can lead to irritation and damage; targeting and delivery, as precise tumor targeting remains difficult due to tumor heterogeneity; and regulatory barriers, which slow clinical translation due to the need for extensive safety and biocompatibility testing. In the future, advancements in targeting techniques using functionalized nanoparticles, combination therapies with treatments like gene therapy or Photodynamic therapy (PDT), applied AI in nanoparticle-based therapies, and personalized nanomedicine tailored to individual tumor profiles offer promising solutions to enhance specificity, efficacy, and patient outcomes.

2. Nanoparticles

Nanoparticles represent a broad and compositionally diverse class of platforms designed to advance therapeutic delivery, improve imaging precision, and enable multimodal interventions. The performance is determined by inherent physicochemical features, such as optical resonance, magnetic responsiveness, and surface charge, along with advances in materials design that allow fine control over particle size, morphology, and surface chemistry. In the following sections, we systematically compare the structural and functional characteristics of various nanoparticle platforms, while elucidating the relationship between their design, therapeutic efficacy, and limitations (Figure 1, Table 1).

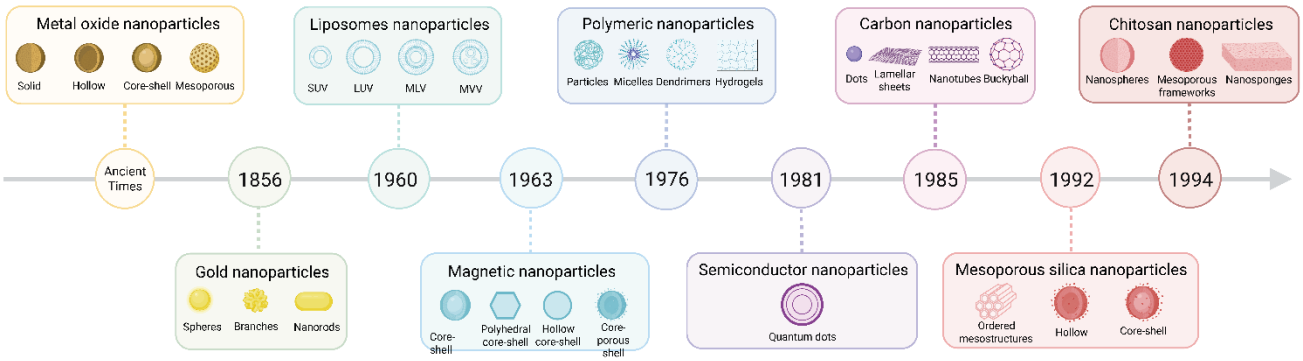

Figure 1. Timeline of Nanoparticles. The timeline illustrates the chronological emergence of major nanoparticle classes, from early metal oxide nanoparticles in ancient times to modern mesoporous silica and chitosan systems. Representative morphologies are shown for each category, including solid, hollow, and core–shell architectures for metal oxides; vesicular structures for liposomes; micelles, dendrimers, and hydrogels for polymeric nanoparticles; quantum dots for semiconductor systems; carbon nanodots, sheets, and nanotubes; and biopolymer-derived chitosan frameworks. The figure highlights the structural evolution and increasing complexity of nanomaterials that underpin their biomedical applications, including those in ocular oncology.

Table 1. Structural and functional characteristics of nanoparticle platforms in ocular oncology. This table summarizes the principal classes of nanoparticles investigated for ophthalmic-related tumors. For each platform, the core structure, key physicochemical properties, surface modification strategies, biomedical functions, and representative applications are listed, together with major advantages and limitations. The comparison highlights how structural design and material composition determine biological performance and therapeutic potential.

Key physicochemical properties	Surface modification strategies	Biomedical functions	Advantages	Limitations
Biomimetic structure; Dual drug-loading capacity; Programmable release; Active targeting	Surface engineering to enhance stability and targeting	Drug delivery; Diagnostic imaging; Combination therapy	High biocompatibility; Multifunctionality; Clinical translatability	Long-term stability; Scalable production; *In vivo* barriers
Biodegradability; Tunable size and surface charge; Programmable release	PEGylation, ligand or antibody conjugation, nucleic acid functionalization	Drug stabilization; Controlled release; Gene delivery; Selective targeting	High payload capacity; Versatile architectures; Customizable kinetics	Degradation byproducts; Complex pharmacokinetics
Surface plasmon resonance (SPR); High electron density; Optical tunability; Radiation enhancement	Conjugation with thiol, amine, cyanide groups; ligand and antibody functionalization	Radiosensitization; Photothermal therapy; Photoacoustic imaging; Biosensing	Stability; Strong optical properties; Facile functionalization	Risk of long-term accumulation; Limited tissue penetration
Superparamagnetism; External magnetic field responsiveness; Magnetic resonance imaging (MRI) contrast enhancement	Polymer coatings, gold shells, folate or antibody targeting ligands	Magnetic navigation; MRI imaging; Magnetic hyperthermia; Biosensing	Magnetic targeting; Imaging–therapy integration; Low remanence	Aggregation risk; Incomplete safety data for long-term exposure
High drug-loading capacity; Tunable pore size; Surface modifiability	Ligand or antibody functionalization, polydopamine gatekeepers, stimuli-responsive coatings	Chemotherapy delivery; Combined therapies; Controlled drug release	Ultra-high loading; Versatile functionalization	Poor biodegradability; Stability affected by complex modifications
Size-dependent emission; High quantum yield; Photostability; Multicolor encoding	Polymer coatings, antibodies, peptides, aptamers	Fluorescence imaging; Multiplex biosensing; Molecular diagnostics	Bright emission; Photostability; Multiplexing ability	Potential heavy-metal toxicity; Incomplete clearance *in vivo*
Positive surface charge; Mucoadhesive properties; Tunable structures	Peptide and aptamer conjugation, PEGylation	Enhanced ocular penetration; Targeted drug delivery; Controlled release	Biocompatibility; Natural abundance; Strong adhesion	Batch-to-batch variability; Limited stability
Strong optical absorption; π–π stacking; Photothermal and photodynamic activity	PEGylation, peptide conjugation, pH- or stimuli-responsive linkers	Photothermal therapy; Photodynamic therapy; Multimodal delivery and imaging	Strong optical/electronic properties; Multifunctionality	Biocompatibility concerns; Potential long-term toxicity
Enzyme-mimicking catalytic activity (Fenton/oxidase-like); Reactive oxygen species (ROS) generation; Photo/thermal responsiveness	Protein coatings, ligand functionalization, magnetic element doping	Chemodynamic therapy; ROS regulation; Photothermal and photodynamic therapy	Strong catalytic activity; Multifunctional integration	Complex synthesis; Long-term toxicology not fully defined

2.1. Lipsomes

As the the most clinically established systems, lipid-based nanomaterials, particularly liposomes, are self-assembled vesicles composed of amphiphilic molecules such as phospholipids and cholesterol, forming a bilayer membrane that encloses an aqueous core [12]. This biomimetic architecture mirrors cellular membranes, conferring exceptional biocompatibility and biodegradability and providing a well-established safety profile in preclinical models, making liposomes a versatile platform for drug delivery [13]. Functional versatility extends beyond structural mimicry: the hydrophobic bilayer accommodates lipophilic drugs, while the aqueous core encapsulates hydrophilic therapeutics, enabling combination therapies and the incorporation of contrast agents for advanced theranostic applications [14]. Targeted delivery is achieved through surface functionalization with ligands, which enhances receptor-mediated uptake, as demonstrated in HER3-targeted systems that increase tumor accumulation. Stimuli-responsive designs allow controlled release in response to pathological cues, such as acidic pH or elevated enzyme activity, while advanced modifications—including mitochondria-targeting motifs—can modulate cellular metabolism and synergize with treatments such as radiotherapy to remodel the immunosuppressive tumor microenvironment [15]. Favorable tissue penetration and retention support effective localized administration, with demonstrated success in intravesical therapy for bladder cancer [16] and ocular delivery for retinoblastoma [17].

By combining biomimetic structure, dual drug-loading capacity, programmable release, and active targeting, liposomes provide a highly adaptable and clinically translatable platform [14]. Although challenges remain in long-term stability, scalable production, and navigating complex *in vivo* barriers, advances in surface engineering and formulation design continue to enhance their performance [16].

2.2. Polymer nanoparticles

Building upon these biomimetic vesicles, polymer-based carriers introduce greater structural versatility and programmable release functions [18,19]. Through molecular engineering and self-assembly, their behavior *in vivo* can be finely adjusted—modulating pharmacokinetics, release kinetics, and targeting to meet the demands of ophthalmic oncology [20]. Despite their structural diversity, these systems share a common goal: stabilizing drugs, increasing payload capacity, and improving therapeutic precision while limiting off-target effects [21]. Five main classes—polymeric nanoparticles, micelles, dendrimers, hydrogels, and nucleic acid nanostructures—illustrate this breadth.

Among them, polymeric nanoparticles are the most extensively studied [22–24]. Produced from natural or synthetic polymers using techniques such as emulsification, gelation, or self-assembly, they frequently adopt a core–shell configuration suited to encapsulating hydrophobic agents [25,26]. Their biodegradability supports sustained release, while particle size and surface charge influence biodistribution and clearance [18,27]. Surface modifications add further control, enhancing stability and enabling receptor-mediated targeting [28]. Polylactic acid-hydroxyethyl acid (PLGA) nanoparticles exemplify this versatility, accommodating a wide range of chemotherapeutics and gaining tumor affinity through surface conjugation [26,29]. Natural polymers extend these benefits: chitosan-based carriers exhibit strong mucoadhesion and tissue penetration for non-invasive ocular delivery [30,31], while hyaluronic acid systems exploit CD44 receptor overexpression to achieve selective uptake by tumor cells [32,33].

Other polymer architectures bring complementary capabilities to the delivery toolbox. Polymeric micelles, self-assembled from amphiphilic block copolymers, use hydrophobic cores to encapsulate insoluble drugs while hydrophilic shells extend circulation time and improve bioavailability [21,22,34]. Dendrimers, with their precisely branched and monodisperse frameworks, provide dense surface functionalities that accommodate drug conjugation, PEGylation, and stimuli-responsive linkers, thereby supporting both high loading efficiency and controlled release [35]. Hydrogels, constructed as cross-linked networks of hydrophilic polymers, act as local reservoirs: they absorb substantial amounts of water and enable sustained release, reducing dosing frequency in long-term therapy [36,37]. Nucleic acid nanostructures, assembled from DNA or RNA, integrate vehicle and payload in one entity by shielding nucleic acids from enzymatic degradation while permitting precise gene-based interventions [38]. Together, these diverse polymer platforms illustrate the adaptability of nanomaterials in drug delivery.

2.3. Gold nanoparticles

Inorganic nanostructures expand functionality further, with noble metals exemplifying optical and radiation-based enhancements. Gold nanoparticles (GNPs) are a typical class of functional nanomaterials, remarkable for their unique optical behavior, high surface reactivity, exceptional stability, and tunable morphologies [39]. Their intrinsic bio-inertness, when combined with appropriate surface modifications, minimizes immunogenicity and enhances biocompatibility, facilitating safe and effective *in vivo* applications [40]. The high electron density of gold further enables efficient absorption of ionizing radiation, amplifying photoelectric effects and Compton scattering to generate cascades of secondary electrons and highly localized energy deposition—a “high-Z” property that underpins their effectiveness as potent radiosensitizers [1,41].Under incident light resonant with the collective oscillation of conduction electrons, GNPs exhibit surface plasmon resonance, producing intense absorption and scattering at defined wavelengths [42]. By precisely controlling particle size, shape, and the surrounding dielectric environment, SPR properties can be finely tuned to optimize performance in colorimetric sensing, photothermal therapy, and photoacoustic imaging [43,44]. The gold surface also provides robust chemical affinity for thiol, amine, and cyanide groups, enabling stable conjugation with targeting ligands, therapeutic agents, and biocompatible coatings [45].

This combination of optical tunability, radiation enhancement, and facile functionalization establishes GNPs as foundational building blocks for advanced targeted drug delivery, functional biosensing, and integrated theranostic platforms that simultaneously support precise diagnosis and therapy [46].

2.4. Magnetic nanoparticles

While gold nanoparticles exemplify the power of optical tuning and radiosensitization, magnetic nanomaterials, particularly iron oxide nanoparticles exhibiting superparamagnetism at the nanoscale, further extend functionality and underpin broad biomedical utility by combining rapid responsiveness to external magnetic fields with adaptable surface chemistry and favorable biocompatibility [47]. Superparamagnetism emerges when particle sizes fall below a critical threshold (typically < 20–30 nm), producing strong magnetization under an applied field while virtually eliminating residual magnetization upon field removal [48]. This property prevents irreversible aggregation and underpins their dual role as magnetic targeting vehicles and MRI contrast agents, enabling guided accumulation in diseased tissue

followed by prompt dispersion to minimize vascular obstruction [49]. When subjected to alternating magnetic fields, these nanoparticles dissipate energy through Néel and Brownian relaxation, generating localized heating [50]. Controlled magnetic hyperthermia raises intratumoral temperatures to 41–46 °C, selectively triggering apoptosis or necrosis in malignant cells while sparing surrounding healthy tissue [51].

In addition to their magnetic responsiveness, certain iron oxide nanoparticles exhibit intrinsic enzyme-mimicking activity, catalyzing hydrogen peroxide decomposition and facilitating substrate oxidation that produces detectable colorimetric changes [52]. Leveraging this peroxidase-like behavior, researchers have developed ultrasensitive, visually readable biosensors capable of identifying tumor cells or molecular biomarkers with high specificity [53]. Further optimization of physicochemical performance is achievable through surface engineering: encapsulation with silica, noble metals such as gold, or polymers including Pluronic F127 and polyvinylpyrrolidone improves colloidal stability and biocompatibility [54,55], whereas conjugation with targeting ligands such as folic acid enhances selective recognition and cellular uptake [56]. Hybrid constructs expand functional versatility even further—gold shells enable photoacoustic imaging, and incorporation of perfluorocarbon facilitates ultrasound imaging—establishing a foundation for multimodal theranostic applications that seamlessly integrate diagnosis, targeted delivery, and localized therapy [17,48].

2.5. Mesoporous silica nanoparticles (MSNs)

Mesoporous silica nanoparticles, with their ordered pore networks, large surface area, and highly variable surface chemistry, ulteriorly enhance structural tunability [9]. Their well-defined mesoporous framework (2–10 nm) affords substantial pore volume, enabling efficient encapsulation of chemotherapeutics such as carboplatin, topotecan, and doxorubicin, and supporting remarkably high drug loading [57]. Surface functionalization further expands their utility: conjugation with antibodies or small-molecule ligands promotes receptor-mediated endocytosis, thereby enhancing recognition and uptake by retinoblastoma cells [6]. In addition, MSNs can be engineered for stimulus-responsive release—exemplified by pH-sensitive polydopamine gating—or combined with near-infrared photothermal therapy to achieve synergistic chemo-photothermal effects [57]. Collectively, these design features allow MSNs to deliver drugs with precision, improve therapeutic efficacy, and minimize off-target toxicity in ocular tumor therapy.

2.6. Quantum dots (QDs)

Semiconductor nanoparticles, particularly quantum dots, form a class of nanomaterials whose optical and electronic behavior is governed by quantum confinement [58]. Their combination of size-dependent emission, high signal fidelity and capacity for multiplexed readout has driven widespread interest in applications such as tumor imaging, liquid biopsy and point-of-care diagnostics [59,60]. When particle dimensions approach or fall below the exciton Bohr radius, bulk electronic bands split into discrete energy levels; as a result, emission wavelength can be tuned continuously from the ultraviolet to the near-infrared by varying nanocrystal size while keeping composition constant [61]. This spectral control enables robust multicolor encoding and simultaneous detection schemes that are not achievable with conventional organic fluorophores [62].

Quantum dots also offer a favorable photophysical profile: high photoluminescence quantum yield, large absorption cross-sections, narrow and symmetric emission peaks, and pronounced resistance to photobleaching [63]. These attributes yield bright, stable signals suited to prolonged imaging and real-time monitoring [64]. The QD surface is readily engineered to provide function: conjugation to antibodies, peptides or aptamers imparts molecular specificity [61] and ligand exchange and polymer coatings enhance colloidal stability and biocompatibility [58]. In addition, QD fluorescence can be modulated by specific chemical or ionic stimuli—for example, redox changes or cation-exchange reactions—which allows quantum dots to serve as active transducers in responsive sensing platforms rather than passive labels [63,64].

2.7. Chitosan nanoparticles

In parallel, polysaccharide-based carriers contribute natural biocompatibility and mucoadhesion for ocular applications [30]. As cationic nanomaterials, chitosan nanoparticles derive their functionality from the protonation of amino groups, which generates a positive surface charge under acidic conditions [65]. This property underpins two critical functions: facilitating self-assembly with anionic biomacromolecules via electrostatic interactions for the construction of complex nanosystems [25], and promoting strong adsorption to negatively charged cell membranes to enhance cellular uptake and delivery efficiency [20].

The utility is further expanded by considerable design flexibility at the materials level. Precise control over particle size, surface charge, and morphology enables the fabrication of diverse architectures, from nanospheres and nanoflowers to mesoporous frameworks and nanosponges with high surface areas, which support a broad spectrum of drug-loading capacities and release kinetics [66]. Surface modifications impart additional functionality; for instance, conjugation with peptides or aptamers confers active targeting [67], while PEGylation enhances stability and circulation time [68], collectively enabling more precise drug release [69]. Such customizable properties enable promising biomedical applications of chitosan nanoparticles. For localized administration, they enhance drug retention and posterior-segment bioavailability while limiting systemic exposure [66]. For systemic delivery, passive accumulation in tumors via the enhanced permeation and retention (EPR) effect can be synergistically combined with ligand-mediated active targeting to achieve greater selectivity [65].

2.8. Carbon nanomaterials

Beyond organic and polysaccharide systems, carbon-based nanomaterials provide a new platform in nanobiomedicine, including zero-dimensional carbon dots, two-dimensional graphene oxide (GO), and soluble nanographenes [70]. A conjugated sp^2-hybridized carbon backbone confers intrinsic optical and electron-transfer properties, while surface functional groups—such as carboxyl and hydroxyl moieties—enhance aqueous dispersibility and offer reactive sites for functionalization, enabling precise tuning of material–biological interfaces [71]. Structural differences among these materials directly shape their functional roles: quasi-spherical carbon dots under 10 nm exhibit strong fluorescence and pH-responsive luminescence, ideal for sensing tumor microenvironments [71]; lamellar GO sheets, with ultrahigh surface area, load aromatic drugs efficiently through π–π stacking and hydrophobic interactions, supporting combinatorial therapies [70]; larger planar nanographenes require peripheral modifications to mitigate π–π aggregation, improve solubility, and ensure biocompatibility [72]. Such structural characteristics underpin their theranostic potential.

Efficient photothermal conversion allows many carbon nanomaterials to generate localized heating for photothermal therapy [73], whereas select species act as photosensitizers, producing reactive oxygen species under irradiation for photodynamic therapy [74]. The high surface area of GO and related nanostructures further supports co-delivery of drugs, targeting ligands, and imaging probes, enabling multimodal diagnostic and therapeutic applications [70]. Additional surface engineering strategies—including PEGylation to extend circulation, conjugation with targeting peptides such as tuftsin, and incorporation of stimuli-responsive linkers—provide controlled, intelligent drug release, seamlessly integrating precision delivery with therapeutic functionality [75].

2.9. Metal oxide nanoparticles

Besides, metal oxide nanoparticles, defined by the coordination of metal elements with oxygen, constitute a broad and chemically versatile class of inorganic nanomaterials [76]. Their properties can be precisely modulated through targeted doping strategies to enhance optical or catalytic performance [77], while morphological control enables synthesis as nanospheres, nanoflowers, mesoporous frameworks, or nanosponges—each conferring distinct surface areas and biointerfacial interaction modes [78]. Further adaptability is achieved through surface functionalization, where protein coatings enhance biocompatibility [78] and conjugated ligands facilitate receptor-mediated uptake [79].

A defining hallmark of these materials is their catalytic and enzyme-mimetic activity. For instance, WO_3/Pt hybrids emulate nicotinamide adenine dinucleotide phosphate (NADPH) oxidase under photoexcitation, promoting intracellular hydroxyl radical production [80]. Similarly, iron- and copper-based particles catalyze Fenton-like reactions in the tumor microenvironment, forming the basis for chemodynamic therapy [76,81]. Cerium oxide nanoparticles (nanoceria) are particularly distinctive for their ability to switch between Ce^{3+} and Ce^{4+} states, exerting context-dependent functions that range from generating reactive oxygen species to providing antioxidant protection [76]. Beyond catalysis, photoresponsive behaviors significantly expand the therapeutic utility of these nanoparticles. CuS and WO_3 efficiently transduce light into heat for photothermal therapy [82], whereas Ce-doped TiO_2 acts as a photocatalyst to generate reactive oxygen species in photodynamic therapy [77]. The incorporation of magnetic elements in certain formulations further extends their applications into the realm of image-guided interventions and multifunctional clinical platforms [83].

2.10. Others

Unconventional nanoparticle systems in ocular oncology exploit physicochemical features that extend beyond those of established platforms. Fluorinated hyaluronic acid nanoparticles exemplify how chemical substitution enhances polymer function, increasing oxygen solubility to relieve tumor hypoxia and augment photoreactivity [84]. Organic chromophores highlight the role of photophysical engineering, with surfactant-stripped naphthalocyanines retaining near-infrared absorption while eliminating cytotoxic residues [85], and ultrasmall clearable nanoparticles designed below the renal clearance threshold to couple efficient energy conversion with rapid excretion [86]. Optical probes extend functionality, with polymer dots offering high quantum yield and photostability for vascular mapping [87], while silicon nanoparticles provide strong emission and straightforward synthesis for sensitive biomarker detection [88]. Material design also enables immunomodulation, as near-infrared II

nanoparticles exploited deep penetration for vascular normalization [89], and platinum–DNA intercalator nanoparticles used covalent binding to trigger cyclic guanosine monophosphate-adenosine monophosphate synthase-stimulator of interferon genes (cGAS–STING) signaling [90]. Bioinspired assemblies further expand the palette, with protein nanocages forming stable architectures capable of barrier penetration and high loading [91]. These examples demonstrate how tailoring molecular composition and structural design—rather than material class—defines the functional reach of emerging nanoparticles in ocular oncology.

If nontraditional material classes expand the range of available nanoplatforms, surface functionalization determines how these structures engage with biological systems. Gold nanoclusters highlight the impact of surface engineering, where biomineralization and intramolecular coreactions accelerate electrochemiluminescence to enable sensitive biomarker detection [92]. Peptide conjugation provides another versatile strategy, as adaptable peptide-functionalized nanoparticles were able to reshape the tumor microenvironment, thereby amplifying the effects of combined radio-immunotherapy [93]. The same principle applies to bioinspired systems, with protein nanocages using precise subunit organization to form stable architectures capable of penetrating mucus and tumor barriers [91]. Even nucleic acid cargoes can be incorporated into functional surfaces, as illustrated by miRNA-211 formulations that stabilized metabolic homeostasis through targeted regulation of lipid biosynthesis [94]. Collectively, these examples underscore that while unconventional chemistries define what nanoparticles are, it is surface modification that dictates what they do—an insight that naturally leads to hybrid and multicomponent platforms where structure and surface are engineered together.

When surface chemistry is combined with compositional complexity, hybrid and multicomponent nanostructures emerge that integrate several functions into a single platform. Lipid–polymer hybrids exemplify this concept, coupling the stability of polymeric matrices with the biocompatibility of lipid shells to achieve synergistic chemo- and photodynamic therapy [95]. Metal–organic frameworks provide another modular strategy, where manganese-based constructs incorporated targeting ligands and therapeutic cargos to enable simultaneous chemodynamic activation and imaging [96]. Supramolecular assemblies broaden this scope, as gold(I)–thiol–peptide complexes form structurally defined “nano-predators” that translate precise control into potent antitumor activity [97], and polydopamine-capped mesoporous carriers combined chemotherapy and photothermal therapy through stimuli-responsive gating [98]. Other hybrids were designed for cascade therapies, such as the “golden cicada” nanoplatform that sequentially disrupted resistance pathways and enhanced the synergy of photothermal and gene therapy [99], or metal–polymer systems that combined chemodynamic enhancement with photothermal ablation [100].

3. Ophthalmic-related tumors

Ophthalmic tumors are uncommon but clinically demanding, arising in vision-critical, immune-privileged tissues where both survival and function must be preserved. Surgery, radiotherapy, and chemotherapy are constrained by ocular barriers, systemic toxicity, and the risk of vision loss. Nanomaterials offer new opportunities by enabling targeted delivery, radiosensitization, phototherapy, and imaging within the eye. Their tunable size and chemistry allow them to navigate protective barriers and exploit tumor-specific vulnerabilities. Here we outline recent progress in nanomaterial strategies for retinoblastoma, uveal

melanoma, optic pathway glioma, and related tumors, with a focus on therapeutic potential and translational challenges (Table 2, Figure 2).

Table 2. Nanomaterials in ophthalmic-related tumors. Comparative summary of ophthalmic-related tumors showing anatomical location, patient population, clinical features, therapeutic barriers, and matched nanomedicine solutions. The table links key challenges with strategies such as enhanced delivery, radiosensitization, phototherapy, barrier penetration, gene/RNA therapy, and theranostics.

Tumor Type	Anatomical location	Patient population	Burden	Clinical behavior	Conventional challenges	Nanomaterial strategies explored
Retinoblastoma	Inner retinal layers	Pediatric	Most common intraocular malignancy	Intraocular, can invade optic nerve and metastasize if untreated	Barrier Toxicity Resistance Imaging gap	PLGA; Micelles Liposomes; Dendrimers Multifunctional NPs Theranostics
Uveal Melanoma	Uveal tract	Adult	Most common intraocular malignancy	High risk of liver metastasis despite local control	Local toxicity Metastasis Light limit Monitoring gap	Au radiosensitizers Targeted delivery PTT platforms; PDT platforms MRI theranostics; PA theranostics
Glioma	Optic nerve; Optic chiasm	CNS tumor	Translational model for ophthalmic oncology	Diffuse infiltration along optic pathway; Low systemic metastasis but local progression	BBB Invasion and resistance Local control Imaging gap	Peptide; FUS; CED siRNA NPs; miRNA NPs PTT nanocomplex; DNA nanocomplex Degradable theranostics
Melanoma	Skin; Conjunctiva	Adult	High incidence; Poor prognosis after metastasis	Rapid growth; Early metastasis; Therapy resistance	Toxicity Hypoxia Resistance Stress adaptation	Albumin–ZnO NPs IL-12 nanogel Thermoelectric nanocatalysts FTO-nanodrugs
Solid Tumors	Systemic; Orbital relevance	All ages	Majority of cancers; Leading mortality	Aggressive; Hypoxic; Heterogeneous	Poor penetration Microenvironment resistance Hypoxia Chemo-toxicity	Ultrasound + DNA NPs Lipid–polymer NPs Peptide systems FA-PEG-PDA-DOX
Lymphoma	Ocular adnexa; Orbit; Systemic	Adult	Systemic important	Indolent or aggressive	Low selectivity Radio-toxicity	Albumin–ZnO NPs NP radiosensitization
Sarcoma	Bone; Soft tissue; Orbit	Children (osteosarcoma); Adults (soft tissue)	Aggressive; Relapse risk	Invasive; Metastatic	Chemo-toxicity Poor bone penetration	Microalgal DOX carriers Bone-targeted NPs

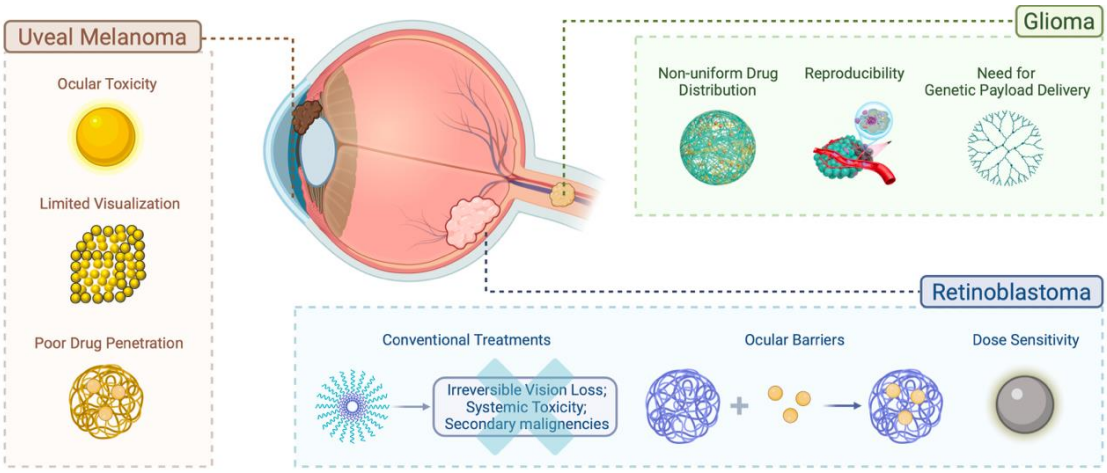

Figure 2. Ophthalmic-related Tumor Treatments Improved by Nanoparticles. Illustration showing representative pathological locations and therapeutic challenges associated with uveal melanoma, glioma, and retinoblastoma. Uveal melanoma is characterized by ocular toxicity, poor drug penetration, and limited visualization; glioma by non-uniform drug distribution, reproducibility issues, and the need for genetic payload delivery; and retinoblastoma by systemic toxicity from conventional treatments, ocular barriers, and dose sensitivity. These challenges highlight the unmet needs motivating the development of nanoparticle-based strategies for targeted, safe, and effective therapy in ophthalmic oncology.

3.1. Retinoblastoma

Retinoblastoma is the most common intraocular malignancy in children, presenting early in life and demanding therapies that ensure survival without sacrificing vision or imposing long-term toxicity. Reviews emphasize the dual challenge of tumor eradication and functional eye preservation [101]. Recent work on functionalized nanosystems, such as polymeric micelles, underscores that therapeutic design must align with the physiology of the developing eye [21].

Nowadays, clinical updates confirm that despite progress, conventional approaches still carry heavy burdens and highlight the need for safer, more effective strategies [102]. At the same time, broader perspectives identify nanomedicine as a promising complement, stressing its relevance to pediatric oncology [31]. Conventional treatment of retinoblastoma—enucleation, systemic chemotherapy, and external beam radiotherapy—is limited by irreversible vision loss, systemic toxicity, and the risk of secondary malignancies. Even local chemotherapy faces challenges nanomaterials directly address its obstacles. Polymeric carriers such as PLGA and micelles improve stability and sustain intraocular release, with notable examples including surface-modified melphalan nanoparticles [26] and carboplatin-loaded surface modified ones [103]. Peptide-conjugated gold nanoparticle inhibits p53-HDM2 interaction in retinoblastoma. Liposomes and dendrimers offer complementary advantages in sustained exposure and intracellular delivery, as demonstrated by liposomal chemotherapeutics [104]. Chitosan-based and receptor-targeted carriers further enhance tumor selectivity, from folate-modified silica nanoparticles [6] to transferrin constructs [54]. Metallic and hybrid nanoparticles expand therapeutic options, such as silver [105], exert cytotoxicity via oxidative stress. Multimodal theranostic platforms integrate therapy with imaging and monitoring [79].

The clinical potential of nanomaterials in retinoblastoma must be weighed against safety and distribution concerns. Biodistribution studies of surface-modified chitosan nanoparticles reveal that functionalization alters tissue penetration and clearance, factors critical for optimizing ocular delivery while minimizing systemic exposure [66]. Toxicological assessments further show that some platforms, including superparamagnetic iron oxide nanoparticles, can exert measurable cytotoxic effects in retinoblastoma cells, emphasizing the need for careful dose control and material selection [106]. These findings underscore the dual imperative in pediatric oncology: ensuring therapeutic efficacy while safeguarding long-term ocular and systemic safety. For translation into the clinic, reproducibility, biocompatibility, and rigorous preclinical modeling must accompany innovation, especially in children where developmental risks heighten the importance of safety margins.

3.2. Uveal melanoma (UM)

Uveal melanoma is the most common intraocular malignancy in adults and the leading cause of eye cancer–related death. Local control with enucleation, brachytherapy, or proton beam radiotherapy is effective, yet metastasis—most often to the liver—remains largely untreatable [102]. Molecularly, UM is defined by activating GNAQ/GNA11 mutations and frequent BAP1 loss, which drive tumor progression and immune evasion [45]. Despite these insights, systemic therapies have shown little benefit, underscoring UM as both a clinical challenge and a model for testing nanomedicine strategies.

Local control in uveal melanoma has long relied on plaque brachytherapy, yet ocular toxicity and limited systemic benefit remain major drawbacks. Dosimetry studies highlight the delicate balance between tumor coverage and collateral damage, and they provide the rationale for radiosensitizers that can sharpen dose deposition [41,107]. Building on this, Monte Carlo simulations [108] and preclinical models [109,110] demonstrate how gold nanoparticles can significantly enhance plaque efficacy without raising background exposure. Photo-based nanotherapies extend this precision. GNP-assisted electron brachytherapy with Ru-106 plaques shows promise for superficial ocular cancers [111]. Gold nanocages and nanostars have been engineered for photoacoustic imaging and plasmonic photothermal therapy, producing both high-contrast visualization and effective cytotoxic heating [39,112]. Near infrared (NIR)-II probes [113,114] further broaden photodynamic options, offering deeper light penetration and controlled ablation. Drug delivery platforms are another major focus. Polymeric and chitosan composites improve penetration and sustained release [25]. Functionalized systems enhance selectivity, from CD44- [32] targeted carriers to aptamer-guided delivery [115]. Stimuli-responsive and organelle-targeting designs refine release and cytotoxicity, including pH/ROS-sensitive micelles [7] and mitochondria-directed constructs [116]. Finally, theranostic nanomedicines combine therapy with imaging guidance. Dual-mode MRI/optical probes and photoacoustic systems enable real-time treatment monitoring while delivering cytotoxic payloads [116]. These advances illustrate how nanomaterials address UM's therapeutic ceiling: refining brachytherapy, expanding phototherapy, enabling targeted drug delivery, and creating multifunctional theranostics.

Translating nanomaterials into uveal melanoma therapy requires equal focus on safety and feasibility. Gene-targeted carriers, such as OUM1/PTPRZ1 silencers, show precision potential but raise concerns over off-target and genomic safety [96]. Theranostic systems that merge MR/optical imaging with therapy exemplify translational promise, yet demand reproducibility and safety validation before

clinical use [74]. These examples underscore that beyond efficacy, UM nanomedicines must prove safe, reproducible, and immunologically compatible to advance toward clinical adoption.

3.3. Optic pathway glioma (OPG)

Optic pathway glioma is a neoplasm arising from glial cells within the optic pathway, encompassing the intraorbital, intracanalicular, and intracranial segments. Its presentation is marked by visual decline and proptosis as the chief and often initial symptoms. Imaging studies demonstrate their complex distribution and highlight how microenvironmental interactions undermine conventional treatment [117,118]. Mapping of eye–brain vascular connections shows shared anatomical routes that influence drug delivery [87].

The treatment of OPG is restricted by the blood–brain tumor barrier (BBTB), which blocks systemic agents and limits efficacy. Peptide-based carriers [119] and focused ultrasound [120] have been shown to transiently open this barrier, enabling entry of therapeutic nanocarriers. Building on this, DNA-based nanocomplexes [121] and convection-enhanced delivery [122] provide improved tumor penetration and more uniform drug distribution. These approaches have successfully delivered cisplatin and genetic payloads in preclinical glioma models. Nanomaterials also advance gene and RNA-based strategies. Viral and non-viral systems facilitate widespread gene transfer [123], while dendrimers improve targeting of tumor-associated macrophages [124] and siRNA delivery [125] to oncogenic pathways. Beyond delivery, nanoplatforms broaden therapeutic modalities. Interstitial photothermal therapy generates durable tumor control [126], while nanoparticle-enabled modulation of microRNAs restores metabolic balance in resistant glioma cells [94]. These strategies show how nanomaterials can bypass glioma's structural barriers, reprogram its molecular drivers, and introduce new energy-based therapies.

Clinical translation of OPG nanotherapies depends on stability, safety, and reproducibility. Biodegradable carriers can distribute broadly in brain tumors while maintaining controlled, safe transgene expression [127]. Yet added efficacy often comes with added risk: survivin-targeted carriers enhance chemotherapy but also amplify cytotoxicity, underscoring the need for strict dose control [128]. Multifunctional nanoparticles that combine imaging and therapy raise further challenges of reproducibility and regulatory clearance [48]. These findings highlight that success in OPG—and by extension in glioma—requires not just barrier penetration and efficacy, but rigorous safety validation and scalable, reliable design.

3.4. Periorbital tumors

Periorbital tumors share pathological types with systemic cancers such as melanoma, lymphoma, and sarcoma, making progress in these fields directly relevant to ophthalmic oncology. The invasion patterns, immune evasion, and stromal barriers that complicate therapy in systemic tumors closely mirror those in ocular disease. Tracking nanomaterial-based advances in these tumors thus offers practical guidance for ophthalmic applications, highlighting strategies that improve penetration, reduce toxicity, and address recurrence.

Melanoma arises most commonly in the skin but can also involve ocular tissues such as the conjunctiva, linking systemic and ophthalmic oncology. It affects a wide age range and contributes to a substantial global cancer burden, with poor outcomes once dissemination occurs [78]. Clinically, it is aggressive, showing rapid growth, early metastasis, and marked resistance to standard therapies [52,129].

Chemotherapy and radiotherapy provide only modest benefit, while targeted therapies often fail due to adaptive resistance [74]. These limitations have motivated nanomaterial strategies that exploit melanoma's distinct microenvironment. Albumin-coated zinc oxide nanoparticles demonstrate selective cytotoxicity through biocompatible oxidative stress [78], and innovative designs target metabolic and stress pathways, including thermoelectric nanocatalysts for photoresponsive cytotoxicity [81] and FTO-targeting nanodrugs that induce disulfide stress [115]. Comparative reviews emphasize that such approaches not only provide direct therapeutic benefit but also establish melanoma as a model for understanding how nanomedicine can overcome resistance and heterogeneity in solid tumors.

Solid tumors, which include a broad spectrum of carcinomas and sarcomas, remain the dominant form of cancer globally and provide key lessons for ophthalmic oncology. They affect diverse patient populations and contribute substantially to cancer mortality [130]. Clinically, solid tumors exhibit rapid growth, stromal remodeling, and hypoxia, all of which create diffusion barriers and limit therapy [18]. Conventional approaches are often undermined by inadequate drug delivery and heterogeneous responses [91]. Nanomaterials are being developed to overcome these barriers. Ultrasound-assisted DNA nanoparticles improve gene transfer into resistant tumor tissue [120], while hybrid lipid–polymer carriers and peptide-based systems modulate the tumor microenvironment to enhance penetration and reduce resistance [95,131]. Stable nanoplatforms integrate therapy with imaging [132], and multifunctional constructs such as FA-PEG-PDA-DOX deliver chemotherapy with high precision and reduced systemic toxicity [133]. Collectively, these findings underscore how nanomaterials address fundamental barriers of solid tumors, providing principles that can be directly applied to ophthalmic cancers.

Although less common in the eye, lymphoma and sarcoma provide additional perspectives for nanomaterial-based strategies in oncology. Primary ocular lymphomas are rare but clinically challenging, and systemic lymphomas demonstrate the potential for nanoparticle-assisted radiosensitization [107]. Sarcomas, including osteosarcoma, highlight another facet of solid tumor resistance—aggressive invasion and protection within dense bone tissue. Conventional chemotherapy for these tumors is limited by toxicity and inadequate penetration. Nanomaterials address these barriers by offering targeted delivery, for microalgal carriers improve doxorubicin transport in osteosarcoma [134], while bone-targeted fluoropeptide nanoparticles inhibit growth while localizing treatment to skeletal lesions [135]. Together, lymphoma and sarcoma models illustrate how nanomedicine can enhance radiotherapy and drug localization in anatomically protected cancers, offering translational lessons for ophthalmic tumors where barriers and toxicity similarly constrain treatment.

4. Biomedical functions and applications of nanoparticles

The potential of nanomaterials in ophthalmic oncology is defined less by their composition than by the biological functions they can achieve. Recent advances show how nanoparticles enhance diagnostic resolution, enable precise drug and gene delivery, and activate therapies through light, radiation, or local biochemical cues. In retinoblastoma, nanotechnology has been recognized as both an opportunity and a challenge for clinical translation [101], while broader surveys of uveal melanoma emphasize how nanomedicine is reshaping strategies for both diagnosis and treatment [136]. At the same time, emerging platforms such as catalytic nanozymes extend applications to oxidative regulation and biosensing [137]. This section examines these diverse functions in sequence, beginning with cancer diagnosis, progressing

through therapeutic modalities, and concluding with additional applications that expand the scope of nanomedicine in ocular tumors (Figure 3).

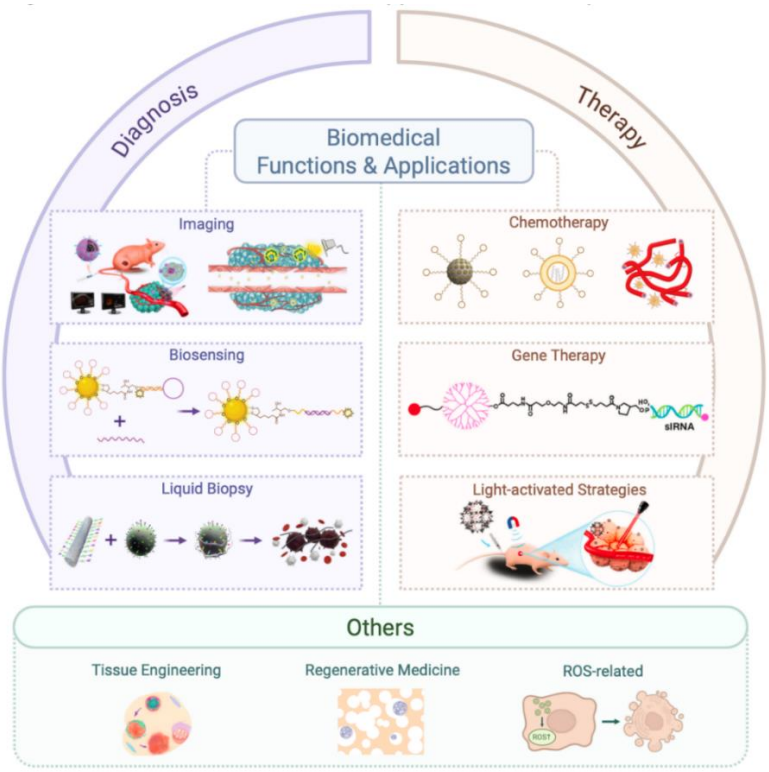

Figure 3. Biomedical Functions and Applications of Nanoparticles. Schematic overview illustrating the multifaceted biomedical roles of nanoparticles across diagnostic and therapeutic domains. On the left, nanoparticles enhance diagnosis through advanced imaging, biosensing, and liquid biopsy technologies that improve sensitivity, molecular precision, and noninvasive detection. On the right, nanoparticles enable therapy by facilitating chemotherapy, gene therapy, and light-activated strategies such as photothermal and photodynamic treatments. The lower panel summarizes other biomedical applications, including tissue engineering, regenerative medicine, and ROS-related modulation, which broaden the impact of nanomaterials beyond conventional cancer management.

4.1. Cancer diagnosis

Reliable early diagnosis remains a major obstacle in managing ophthalmic tumors such as retinoblastoma and uveal melanoma. Conventional imaging and biopsy approaches often lack the sensitivity or specificity to detect disease at an early stage, when interventions would be most effective. Nanomaterials offer a solution by amplifying weak molecular signals, improving contrast in established imaging modalities, and enabling noninvasive detection strategies. Broader advances in oncology show how nanoparticle-based systems can redefine imaging and biomarker analysis [117], while applications in uveal melanoma and retinoblastoma demonstrate their capacity to deliver precise and clinically relevant information [136,138]. Together, these developments establish nanomaterials as a foundation for next-generation diagnostic technologies in ophthalmic oncology.

4.1.1. Imaging

Imaging is fundamental in ophthalmic oncology, yet conventional modalities often struggle to detect tumors at early stages or to provide molecular detail. Nanoparticles offer solutions by acting as precision contrast agents that amplify signals, extend imaging depth, and incorporate therapeutic functions. Broader work in neuro-oncology highlights their potential to transform clinical imaging [117], while retinoblastoma studies show how nanoparticle delivery systems are being integrated into both diagnosis and treatment [19]. This versatility is evident across established imaging platforms as well as emerging approaches.

Traditional structural imaging techniques such as MRI and ultrasound have been upgraded by nanomaterials to improve both clarity and functionality. Mn(II)-Metal organic framework (MOF) nanoparticles conjugated with Ethoxybenzyl-poly(ethylene glycol) (EOB-PEG) holds great promise for the development of MRI hepatobiliary-specific contrast agents [139]. Silica nanoparticles functionalized for retinoblastoma improved MRI contrast [9], and gadolinium-encapsulated glycol chitosan nanoparticles produced strong T1 signals with low background [68]. Hybrid gold–gadolinium nanoprobes extended these capabilities to CT/MR lymphography, aiding accurate staging [140]. Parallel advances in ultrasound have introduced nanoparticles that generate stable echogenic signals and can release drugs under acoustic stimulation [3]. Further integration with focused ultrasound or photoacoustic imaging has enabled imaging-guided interventions in retinoblastoma [48]. Gold nanocages and thin-layer protected AuNPs pushed photoacoustic imaging into ophthalmic applications, offering higher resolution and deeper visualization than conventional ultrasound [14,141]. These examples show how nanoparticles extend structural imaging from simple visualization into platforms capable of real-time monitoring and therapy guidance.

Optical methods, long used for surface-level tumor detection, have also been redefined by nanomaterials. NIR-II bioconjugates enable precise, non-invasive follicle and tumor imaging [142]. Polymer nanoparticles producing persistent afterglow in the near-infrared enabled sensitive tumor tracking *in vivo* [58,60], aza-boron-dipyrromethene (aza-BODIPY) liposomes offered stable emission [12], and fluorescent polymer dots mapped ocular and brain vasculature at high resolution [87]. Quantum-dot and hybrid NIR-II systems extended this reach to specific ocular tumors [114]. These molecularly precise platforms provide the foundation for multimodal imaging, where different signals are combined in single constructs. Surfactant-stripped naphthalocyanines supported multimodal theranostics with upconversion guidance [85], while laser-activated nanoparticles enabled simultaneous imaging and gene therapy in retinoblastoma [8]. Other systems merged imaging with therapy through manganese-based MOFs for uveal melanoma [96], multifunctional polymers for retinoblastoma [143], and MOF-based [73] designs linking imaging with immunotherapy. In this way, nanomaterials connect optical sensitivity with multimodal integration, moving imaging closer to personalized treatment monitoring.

Translation into clinical workflows requires not only better imaging but also intraoperative guidance. Nanoparticles are beginning to play this role: carbon nanomaterials have been used to mark lesions for surgical resection [144], and up-converting nanoparticles provided real-time fluorescence to aid ovarian cancer surgery [145]. Beyond the operating room, other nanomaterial platforms expand imaging into functional and therapeutic monitoring. ATR-FTIR spectroscopy enabled label-free assessment of therapeutic response [2], hafnium oxide nanocrystals offered dual imaging and radiotherapy enhancement [146], and nanoshells provided surface-enhanced Raman scattering with on-demand

activation [147]. These approaches illustrate a shift from static images toward integrated diagnostic–therapeutic systems, with nanomaterials as the common enabler.

4.1.2. Biosensors

Detecting ophthalmic tumors at an early stage is still difficult. Conventional assays often fail to pick up rare tumor cells or low-abundance biomarkers. Nanomaterials change this by amplifying weak molecular signals and converting them into clear outputs. In uveal melanoma and retinoblastoma, multifunctional nanoparticles have already shown potential in both molecular assays and imaging, pointing to their value as diagnostic tools [136,138].

Gold nanoparticles (AuNPs) are central to optical biosensors because their plasmonic properties generate strong color changes or scattering signals. These features allow direct visualization of cancer targets without complex instruments. Examples include aptasensors that reveal tumor cells through AuNP aggregation [43] and dark-field imaging of individual probes for sensitive microRNA detection [148]. Moreover, Au cluster probes allow naked-eye visualization of membrane type 1 matrix metalloproteinase (MT1-MMP) expression, representing a rapid, simple, and practical diagnostic tool for tumor-associated protein profiling [149]. Oligonucleotide-functionalized AuNPs detect viral RNA [150], while catalytic remodeling of nanoparticle surfaces improves detection down to the single-cell level [151]. These optical platforms highlight how nanoscale materials turn molecular recognition into rapid, visible signals. Colorimetric probes build on the same principle but focus on simple, accessible formats. AuNP combined with isothermal amplification enables highly sensitive viral gene detection [152]. Paper-based and urine-based assays extend these tools to population-level screening: p16 immunosensors for cervical cancer [153], PCA3 assays for prostate cancer [154], and RNA-conjugated AuNPs for gastric cancer [155]. Probes for metabolic markers, such as normetanephrine [156] and hypercalcemia [157], show that nanomaterials can support diagnostic readouts across diverse disease contexts. These assays demonstrate how nanoparticle colorimetry delivers low-cost, scalable tests suited for clinical use.

Advanced nanosensors integrate multiple signal channels to boost sensitivity and reliability. Plasmonic enzyme-linked immunosorbent assay (ELISA) using silver nanostructures detects prostate-specific antigen (PSA) at high sensitivity [158], while enzyme-mimetic nanoclusters provide stable visual readouts [159]. Silver nanoparticles also developed a rapid (10 s) colloidal colorimetric assay for RNA biomarkers [160]. Multiplexed systems, such as AuNP microarrays for lung cancer markers [161], dual-mode test strips for breast cancer proteins [56] allows simultaneous detection of several targets. Electrochemical and magnetic components add further depth: dendritic palladium-boron-phosphorus (PdBP) nanospheres detect HPV16 E6 proteins [162,163], and multifunctional magnetic nanoparticles combine optical and fluorescent sensing for breast cancer cells [53]. Exosome assays using Au@PdPt [164] and iridium aggregates [165] show how engineered nanosensors can push diagnostic performance toward clinical-grade accuracy.

Other biosensing strategies reveal the breadth of nanomaterial applications. For example, surface-enhanced Raman scattering (SERS) and Localized Surface Plasmon Resonance (LSPR)/SPR sensors utilize nanoscale field enhancement for label-free, sensitive detection of biomolecules [166,167], nanomaterial-based Bio-FETs transduce binding into electrical signals for real-time monitoring [168] and nanopore sensors achieve single-molecule resolution by measuring ionic current modulations during molecular translocation [169]. These tunable nanomaterials extend biosensing applications from

environmental monitoring to disease diagnosis [170,171]. As for oncology, Phage-assisted systems enable naked-eye counting of microRNAs at attomolar concentrations [172], and nuclease-amplified AuNP assemblies visualize circulating microRNAs at sub-femtomolar levels [173]. Semiconducting polymer nanoparticles achieve ultrasensitive afterglow imaging of metastatic tumors [60], while fluorescent paper sensors allow ratiometric readouts from urine samples [64]. Electrochemiluminescent nanoclusters [92], enzyme-free amplification for circulating tumor cells [59], and radiation-responsive nanosensors [174] expand diagnostics into therapy monitoring. Clustered regularly interspaced short palindromic repeats (CRISPR)-coupled nanoparticles represent a major leap, enabling precise detection of exosomal and microRNA biomarkers with high programmability [175,176]. Dual-colorimetric kits for circulating miRNAs [177] add further clinical relevance. These examples underscore how nanomaterials act as active transducers—converting molecular events into reliable diagnostic signals—and are reshaping how ophthalmic and systemic cancers can be detected.

4.1.3. Others

Beyond biosensors and imaging, nanomaterials are opening new diagnostic frontiers. These platforms capture signals that conventional methods often miss, from circulating tumor cells to subtle metabolic changes. By converting weak biological or optical cues into clear outputs, they extend cancer diagnostics into liquid biopsy, molecular sensing, and beyond.

Liquid biopsy illustrates this shift. Magnetic nanowires captured rare circulating tumor cells with ultrasensitivity [49], and extracellular vesicle profiling in retinoblastoma revealed resistance pathways with direct clinical relevance [178]. Related approaches include telomerase sensing with TiO_2 nanotubes [179], SERS devices for breath-based cancer diagnostics [180], and aqueous humor fingerprinting analyzed by machine learning for retinoblastoma monitoring [181]. Optical hybrids build on the same idea: SERS–colorimetric sensors for MUC1 [182], dual-mode fluorescence–colorimetric platforms for breast carcinoma [63], and phthalocyanine–blue nanoparticles for direct white-light visualization of tumors [183]. These systems show how nanomaterials convert faint biochemical or spectral signatures into actionable diagnostics.

Other platforms move beyond detection to combine diagnosis with therapy. Lipid carriers designed for uveal melanoma doubled as diagnostic trackers [184], and albumin–macrocyclic conjugates enabled precise radionuclide delivery [185]. Reviews of retinoblastoma and melanoma emphasize this trend toward multifunctional nanoplatforms [102], while broader work suggests similar diagnostic potential across systemic diseases [186]. These studies mark a transition: nanomaterials are turning cancer diagnosis from a static test into a continuous process that can guide, monitor, and complement treatment in real time.

4.2. Cancer therapy

Conventional treatments for retinoblastoma and uveal melanoma risk severe vision loss and systemic toxicity. Nanomaterials address these challenges by enabling localized delivery, reducing off-target damage, and combining therapy with diagnostic functions. In retinoblastoma, nanoparticle systems are being developed to overcome drug resistance and improve intraocular delivery [101,187]. Similar

approaches are advancing melanoma treatment, where nanomaterials enhance therapeutic precision and safety [188].

Nanocarriers that combine targeting with controlled release are transforming chemotherapy for retinoblastoma and uveal melanoma. Ligand-modified systems improve precision. Epithelial cellular adhesion molecule (EpCAM) antibody–linked carboplatin carriers enhanced intraocular delivery [189], and aptamer-functionalized liposomes increased doxorubicin efficacy with reduced toxicity [13]. Stimuli-responsive designs add another layer of control. Hyaluronidase-sensitive nanoparticles selectively released their payload in tumor tissue [129], while enzyme-degradable carriers achieved prolonged therapeutic activity [190]. Sustained-release formulations extend drug exposure and reduce invasive dosing. Cisplatin nanoparticles maintained long-lasting activity against intraocular tumors [122], PLGA-based carboplatin systems slowed release while retaining potency [103], and nanostructured lipid carriers achieved prolonged delivery with good safety [191]. Hydrogels provide an especially effective depot: gemcitabine–paclitaxel composites offered continuous release [192], dendrimer matrices delivered melphalan directly into the vitreous [35], and cascade hydrogels co-released lapatinib in uveal melanoma [33]. Other approaches broaden this toolkit. Curcumin-loaded nanoparticles supported sustained activity in UM [37] and graphene oxide composites enabled stable doxorubicin release [70]. Hybrid systems merge targeting with sustained delivery: albumin nanocages transported doxorubicin to tumors and lymph nodes [193], while long-retention nanocarriers held drugs in tumor tissue for over 120 hours [133]. Recent designs go further, combining release control with microenvironment modulation or immune engagement [194]. Together, these strategies make targeting and sustained release a foundation of nanomedicine in ocular oncology, supporting chemotherapy that is both precise and durable.

Nanocarriers developed specifically for retinoblastoma (RB) and uveal melanoma address the unique challenges of intraocular chemotherapy, such as limited drug penetration and the need for localized, sustained activity. In RB, liposomal and polymeric formulations have shown improved intraocular retention and therapeutic efficacy. For example, multifunctional polymeric nanoparticles enabled combined chemo- and phototherapy [143], while surface-modified PLGA carriers provided prolonged carboplatin activity *in vitro* [103]. Phase-changeable systems added responsiveness, such as Fe^{3+}–tannic acid/paclitaxel nanoparticles designed to release under intraocular conditions [29]. On the other hand, UM therapies have increasingly relied on biodegradable and bioengineered lipid nanocarriers for safe and sustained drug delivery. For instance, chitosan-based carriers achieved enhanced bioavailability with favorable tolerability [66], while lipid formulations improved ocular drug stability and distribution [184]. Injectable hydrogels represent another promising avenue, allowing continuous intravitreal release of chemotherapeutics [36]. Beyond conventional cytotoxic delivery, newer strategies are exploring hybrid and natural-product carriers. Gold nanoparticles conjugated with atrial natriuretic peptide were proposed for chemoresistant RB [40], while metal nanoparticles derived from *Centella asiatica* extracts demonstrated anticancer potential in Y79 cells [195]. Reviews reinforce how RB and UM have become model systems for testing nanocarrier innovations, both as stand-alone therapies and as platforms for multimodal integration [19].

Outside ophthalmic oncology, nanocarriers have transformed systemic cancer drug delivery by improving bioavailability, selectivity, and pharmacokinetic stability. Polymeric nanoparticles such as mPEG–PAE carriers loaded with doxorubicin achieved high tumor cytotoxicity with minimal systemic toxicity (Miryala [196]). Red blood cell membrane–cloaked nanocarriers provided immune

evasion and prolonged circulation, enhancing accumulation at tumor sites [197]. Polymeric micelles incorporating doxorubicin reduced cardiotoxicity while maintaining therapeutic potency [198]. Other designs coupled pharmacologic synergy with nanotechnology, such as BPTES–metformin co-loaded nanoparticles for metabolic inhibition [199] and polymeric systems co-delivering paclitaxel and pigment epithelium–derived factor (PEDF) gene to integrate chemo- and gene therapy [200]. Tumor-targeting chitosan–hyaluronic acid hybrids demonstrated selective uptake and light-triggered release for enhanced drug deposition [201]. Lipid-based or D-α-tocopherol polyethylene glycol succinate (TPGS)-emulsified PLGA nanoparticles improved solubility and bioavailability of poorly soluble anticancer agents [202,203], while amphiphilic hyaluronic acid nanogels provided high oxaliplatin loading and tumor suppression in colon cancer [204]. Collectively, these studies demonstrate how nanoparticle engineering—through surface modification, amphiphilic balance, and biomimetic cloaking—can overcome solubility, stability, and toxicity barriers, establishing a foundation for improved delivery in ocular and systemic tumors alike.

Nanocarriers are increasingly used to deliver genes in retinoblastoma and uveal melanoma, overcoming the instability and safety issues of viral vectors. In RB, polymeric nanoparticles carrying the pigment epithelium–derived factor gene markedly suppressed tumor growth [205], while non-viral carriers enabled delivery of therapeutic plasmids [206] and siRNA [10] in preclinical models. Targeted silencing approaches have also shown promise. Lipid nanoparticles co-delivering siRNAs against VEGF and Bcl-2 reduced angiogenesis and enhanced cytotoxicity [10], and peptide-modified complexes improved siRNA transfection by binding both CD44 and EGFR [207]. Moreover, peptide GE11-polyethylene glycol-polyethylenimine helps targeted gene delivery in laryngeal cancer [208]. Adjunct methods can further boost delivery efficiency. Focused ultrasound enhanced nanoparticle dispersion and improved transfection in otherwise resistant tissues [209]. Expanding beyond DNA and siRNA, newer systems explore RNA-based therapeutics, such as bacteriophage phi29–derived RNA for sensitizing tumors [210] and dendrimer–siRNA conjugates for precise intracellular release [125]. Local anti-PD-1 mRNA NP enhances tumor-infiltrating T cell activity [211]. These studies show how nanocarriers extend the reach of ocular oncology from chemotherapy to genetic modulation, offering new ways to regulate tumor growth and resistance.

Nanocarriers also support light-activated strategies, enabling tumor ablation with high precision. In retinoblastoma, gold nanostructures and other photothermal agents induced selective cell death under near-infrared light [112], while phase-changeable nanoparticles released paclitaxel during heating, producing dual cytotoxic effects [29]. In uveal melanoma, carbonized metal–organic framework nanoparticles integrated imaging, photothermal activity, and immunotherapy into a single platform [73]. Parallel advances in PDT have focused on improving photosensitizer delivery. Chitosan-based nanoparticles increased uptake and efficacy of photosensitizers in RB [69]. Clinical translation has been pursued with nanoformulated Verteporfin, which produced stronger, more targeted PDT than free drug formulations [32]. Hybrid systems further merge PTT and PDT. For instance, dual-target nanoliposomes enabled imaging-guided combination therapy in RB [17], and hyaluronic acid–modified nanocarriers co-delivered doxorubicin and Chlorin e6 for synergistic chemo-PDT activity [22]. Collectively, these studies show how nanocarriers extend into photothermal and photodynamic therapies, offering on-demand, localized treatments that complement chemotherapy and gene therapy in ocular oncology.

Nanomaterials have also been explored as adjuncts to radiotherapy and in other therapeutic roles that extend beyond drug, gene, or light-activated delivery. In retinoblastoma, magnetite nanoparticles

were engineered into a shielding device for plaque brachytherapy to limit radiation damage to healthy tissue [83], while superparamagnetic iron oxide particles showed radiosensitizing potential but also mitochondrial toxicity, highlighting the need for careful control [106]. Nanocarriers have further supported immunotherapy, as in uveal melanoma where drug-loaded platforms were combined with immune modulators to strengthen antitumor responses [191]. Injectable hydrogels have enabled prolonged local chemotherapy, with nanocomposite systems achieving cascade drug release in UM [36]. Natural-product nanomaterials such as *Centella asiatica*–derived particles have added intrinsic anticancer activity against RB cells, underscoring how biogenic carriers can complement synthetic designs [195]. These studies demonstrate the versatility of nanomaterials as radiosensitizers, immune adjuvants, drug depots, and even therapeutic agents, broadening the scope of ophthalmic tumor therapy.

4.3. Further applications

While most research has centered on nanomaterials for direct tumor diagnosis and therapy, their functions in ophthalmic oncology extend further into regenerative support, safety assessment, and oxidative balance. These applications are not primarily cytotoxic but instead enhance treatment environments, mitigate risks, and introduce new diagnostic–therapeutic possibilities. Examples include injectable hydrogels that sustain ocular drug release while protecting surrounding tissue, antioxidant carriers that regulate reactive oxygen species, and toxicity studies that define nanoparticle safety profiles. These directions illustrate how nanomaterials can complement mainstream therapies and expand the clinical toolkit for managing retinoblastoma and uveal melanoma.

Tissue engineering and regenerative medicine approaches illustrate how nanomaterials can improve the ocular environment alongside antitumor effects. Biodegradable carriers such as PEGylated nanoparticles with memantine demonstrated neuroprotection relevant for preserving retinal function during intensive treatments [212]. Hydrogels extend this versatility. Microenvironment-responsive systems were engineered for choroidal melanoma [113] and hybrid afterglow platforms combined imaging with therapy [114]. These designs illustrate how delivery scaffolds can simultaneously treat tumors and support ocular tissue integrity.

Safety evaluation is equally important. ZnO nanoparticles induced cytotoxicity across malignant and normal cells [213], while paclitaxel caused ocular complications in clinical settings [214]. Cases of conjunctival discoloration from silver exposure [215] and studies of iron oxide nanoparticle biotransformation [47] emphasize the need to assess long-term risks. Broader work with nanoplastics in zebrafish further showed transgenerational disruption of cancer-related pathways [216]. These findings underscore that therapeutic potential must be matched with rigorous toxicity profiling.

Nanomaterials possess the dual capability to actively generate ROS for eliminating diseased cells and, conversely, to intelligently scavenge ROS for protecting healthy tissues or halting disease progression [217–219]. Antioxidant carriers such as astaxanthin-loaded lipid nanoparticles modulated Nrf2/Keap1 and NF-κB pathways [220]. In contrast, carbon dots enhanced uveal melanoma progression through ROS-driven mTOR signaling [75], illustrating how oxidative modulation can cut both ways. More advanced systems used ROS generation for sensing and detection, including pH-responsive polymer dots [71] and nanozyme-mediated CRISPR-Cas12a assays for microRNA [175].

Other emerging strategies point toward future directions. Plasmon-mediated nanoparticles were tested for retinoblastoma in vitreous-like models [42], magnetic hyperthermia induced apoptosis in

RB and retinal epithelial cells [51], and celastrol nanomicelles suppressed angiogenesis-driven tumor growth [221]. Biopolymeric carriers improved melphalan penetration across corneal barriers [30], while vesicle-encapsulated composites achieved targeted theranostics in RB [79].

5. Challenges and perspectives

Nanoparticle-based therapies offer powerful tools for ophthalmic tumors, integrating targeted delivery, radiosensitization, and diagnostic imaging. However, their clinical translation is constrained by toxicity concerns, barriers to precise targeting, and slow regulatory approval. At the same time, rapid progress in advanced targeting, multimodal therapies, artificial intelligence, and personalized nanomedicine suggests a future where these obstacles can be overcome. This section outlines the key challenges and highlights the innovations shaping the next phase of development.

5.1. Challenges

Nanoparticle-based therapies show promise for treating ophthalmic tumors but face key challenges. A major gap is the absence of standardized ocular-specific safety protocols for nanomedicines; most current regulatory and safety evaluations follow systemic nanotoxicity guidelines, which do not encompass the unique environment, clearance dynamics, and sensitivity of ocular tissues [222,223]. Ocular toxicity from prolonged nanoparticle exposure, difficulties in targeting and delivery due to the blood-retina barrier and tumor heterogeneity, and regulatory barriers slow clinical adoption. Moreover, nanoparticle behavior in ocular tissues—such as variable biodistribution, potential retinal accumulation, limited penetration through ocular barriers (e.g., blood–retina barrier, inner-limiting membrane), and challenges in tracking clearance—makes it difficult for regulators to define uniform pharmacokinetic and pharmacodynamic profiles [224,225]. The lack of standardized safety protocols and the complexity of nanoparticle behavior in ocular tissues complicate their approval. Addressing these issues is crucial for advancing nanoparticle-based treatments in ophthalmic oncology.

Firstly, ocular toxicity is a significant concern in nanoparticle-based therapies for ophthalmic tumors. While nanoparticles are designed to enhance drug delivery, their prolonged presence in the eye can lead to retinal damage and inflammation. For example, solid lipid nanoparticles used for intravitreal drug delivery raise concerns about oxidative stress and the potential for retinal damage [220]. These concerns emphasize the importance of ensuring the biocompatibility of nanoparticles, as poor clearance could lead to chronic toxicity. Studies have also shown that liposomes and PLGA-based carriers, though promising, need to be carefully evaluated for their safety in the retina and other sensitive ocular structures [190,226]. Therefore, optimizing the design of nanoparticles to ensure safe clearance and minimal toxicity remains an ongoing challenge in the field.

Moreover, targeting and delivering nanoparticles to ocular tumors is complicated by the blood-retina barrier and tumor heterogeneity. Although nanoparticles can be engineered for tumor-specific targeting, achieving precise delivery without affecting surrounding tissues remains difficult. For instance, mesoporous silica nanoparticles show promise for retinoblastoma, but their ability to selectively target tumor cells is still limited [9]. Additionally, the tumor microenvironment complicates treatment, as different regions of the tumor respond differently to nanoparticles. In uveal melanoma, while nanoparticles enhance radiotherapy, ensuring consistent targeting of the tumor is a challenge [109]. Issues like

nanoparticle aggregation and poor cellular uptake further hinder effective drug delivery, limiting the therapeutic impact of these treatments [190]. Overcoming these barriers requires nanoparticles that can improve targeting precision and penetration in ocular tissues for more effective therapies.

Regulatory barriers also present a significant challenge to the clinical use of nanoparticle-based therapies for ophthalmic tumors. A key hurdle is the absence of standardized preclinical testing requirements tailored to ocular nanomedicine; most regulatory agencies rely on systemic nanotoxicology guidelines that do not account for intraocular behavior, long-term retinal exposure, or nanoparticle clearance kinetics [227]. Moreover, safety-validation procedures are not harmonized: there is no consensus on how to assess chronic retinal toxicity, immunogenicity, nanoparticle degradation or accumulation, and long-term biocompatibility for intraocular use [228]. Another barrier is the lack of standardized ocular models—both *in vitro* and *in vivo*—suitable for nanoparticle penetration, biodistribution, and toxicity testing. Animal models commonly used (e.g., rodents, rabbits) differ significantly from human ocular anatomy and physiology, which limits the predictive value of preclinical data for human applications [229]. These challenges highlight the need for more efficient and clear regulatory guidelines that address the unique characteristics of nanoparticle therapies in ophthalmic oncology [226].

5.2. Future directions

While several challenges, such as ocular toxicity, targeting precision, and regulatory barriers, currently limit the clinical use of nanoparticle-based therapies for ophthalmic tumors, future advancements hold the potential to overcome these obstacles. Advanced targeting techniques, combination therapies, and personalized nanomedicine are key to improving the efficacy and precision of treatments. Additionally, artificial intelligence (AI) is poised to enhance nanoparticle design and drug delivery systems, further optimizing targeting accuracy and treatment outcomes.

To begin with, advanced targeting techniques are crucial for enhancing nanoparticle-based therapies in ophthalmic tumors. Mesoporous silica nanoparticles functionalized with anti-MRC2/CD209 antibodies improve tumor specificity in retinoblastoma [5]. Liposome nanoparticles offer precise delivery of drugs like doxorubicin, minimizing systemic toxicity [190]. Glycol chitosan nanoparticles and protein nanocages further optimize targeted delivery, enhancing tumor specificity [65,91]. These advancements are key to improving the precision and safety of ophthalmic tumor treatments.

What's more, combination therapies are gaining momentum in the treatment of ophthalmic tumors, where integrating nanoparticles with other treatment modalities, such as chemotherapy or photothermal therapy, can enhance efficacy [230]. For example, polymeric nanoparticles co-loaded with both sorafenib and PEDF have shown promise in cancer therapy, improving drug delivery and synergistic therapeutic effects [231]. In retinoblastoma, multifunctional nanoparticles that combine chemotherapy and photothermal therapy offer a promising approach for overcoming resistance and enhancing therapeutic outcomes [143]. These innovations in combination therapies will allow more effective, targeted, and personalized treatments for ophthalmic tumors, addressing the limitations of single-modality therapies.

On the other hand, artificial intelligence (AI) is transforming nanoparticle-based therapies for ophthalmic tumors by optimizing nanoparticle design and targeting precision. Machine learning algorithms are being used to enhance the performance of drug delivery systems, including chitosan-based nanoparticles that are optimized for better biocompatibility and targeting efficiency [232]. AI-driven

models also assist in fine-tuning liposome nanoparticles for more effective delivery of drugs like doxorubicin, ensuring precise targeting of tumor cells [233]. Additionally, AI can predict the interaction of nanoparticles with tumor cells, optimizing drug release profiles and enhancing the efficacy of combined therapies [234]. Beyond these applications, AI-based modeling frameworks that integrate text mining and high-throughput experimental data are being used to map relationships among nanoparticle compositions, drugs and biological targets, thereby supporting nanoparticle modeling and prioritizing nanoparticle–drug–tumor combinations for further evaluation in cancer nanomedicine [235]. High-throughput, automated platforms that couple microfluidic synthesis with machine learning models iteratively adjust formulation parameters, such as core material, particle size, surface charge and drug loading, according to readouts of stability, encapsulation efficiency, cellular uptake and pharmacokinetics/pharmacodynamics, enabling predictive optimization of nanoparticle formulation and performance while helping identify active pharmaceutical ingredients that are compatible with specific liposomal or lipid nanoparticle carriers [236]. Looking ahead, by linking these modeling tools with patient-derived imaging and molecular profiles, AI is expected to support personalized nanoparticle delivery systems for ophthalmic tumors, in which formulation, dosing schedule and route of administration are tailored to the individual tumor phenotype and ocular tolerance [235,236]. As AI technology advances, it will provide more efficient ways to design and test nanoparticle therapies, ultimately leading to more effective, targeted treatments for ophthalmic tumors.

Meanwhile, personalized nanomedicine also holds great potential for enhancing nanoparticle-based therapies in ophthalmic tumors. By tailoring treatments to individual tumor profiles derived from tumor tissue and liquid-biopsy samples, where genomic, transcriptomic and proteomic alterations as well as receptor-expression patterns are used to guide the choice of targeting ligands, drug combinations and dosing schedules [237–239], nanoparticles can improve targeting precision and reduce side effects. For example, nanomaterials are being integrated into strategies to overcome treatment resistance in retinoblastoma [178], while nanoparticles are also enhancing therapies for uveal melanoma by addressing tumor-specific needs [188], illustrating how nanosystems can be adapted to patient- or tumor-specific resistance mechanisms and microenvironmental features. Furthermore, diagnostic tools like aptasensors based on semiconductor nanoparticles enable real-time, personalized treatment adjustments [62], and similar micro- and nanodevice-based liquid-biopsy platforms for circulating tumor cells, cell-free DNA and exosomes may allow repeated monitoring of ocular tumor biomarkers and timely modification of nanoparticle regimens in individual patients [240]. Looking ahead, integrating such biomarker-driven stratification with responsive and theranostic nanomedicines, as well as computational and AI-assisted formulation design, is expected to support truly patient-specific nanoparticle formulations for ophthalmic tumors [241].

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Authors' contribution

Conceptualization, X.X. and Q.L.; methodology, J.L. and Z.H.; resources, X.H.; writing—original draft preparation, X.X., Q.L., and Y.Y.; writing—review and editing, X.H. and Y.F.; visualization, X.X.;

supervision, X.H.; project administration, X.H.; funding acquisition, X.H. and Y.F. All authors have read and agreed to the published version of the manuscript.

Conflicts of interests

The authors declare no conflict of interest.

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