Gold Nanoparticle Shape Design for Ophthalmic Imaging and Therapy

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Abstract

Ocular drug delivery presents significant challenges due to the unique and complex anatomical and physiological barriers of the eye. Among the various types of nanocarriers developed, gold nanoparticles have demonstrated considerable promise in overcoming ocular barriers and delivering incorporated drugs through the cornea and conjunctival epithelia. Gold nanoparticles were extensively investigated for the management and diagnosis of ocular diseases, including glaucoma, diabetic retinopathy, and age-related macular degeneration. The properties and functionalities of gold nanoparticles are highly dependent on particle size and shape, which can be easily controlled through various synthesis approaches. Owing to their low toxicity, biocompatibility, tunable optoelectronic properties, and adjustable surface plasmon resonance, the application of gold nanoparticles in ophthalmology have increased significantly in recent years. The current *review* provides the therapeutic and diagnostic ocular applications of gold nanoparticles from a morphology-oriented perspective, highlighting its impact on ocular delivery efficiency and imaging performance, while considering additional parameters such as particle size and surface coating and functionalization.

Keywords

Gold nanoparticles, ophthalmology, morphology, nanospheres, nanorods, nanostars, optical coherence tomography

1. Introduction

According to the WHO, more than 2 billion people suffer from impaired vision in 2019[1,2]. Drug delivery to the eye is challenging because of its distinctive anatomical and physiological barriers. Although these barriers protect the eye against toxins and microorganisms, they render it an immune-privileged organ, posing significant challenges for the effective management of eye diseases. Several ocular delivery routes are being investigated to deliver various therapeutics, including topical, subconjunctival, subretinal, and intravitreal (**Figure 1**)[3]. These approaches vary in terms of targeted regions, applied volumes, invasiveness, and advantages or limitations. Various periocular administration routes have been explored as alternatives to the invasive intravitreal injections. However, conventional ocular dosage forms such as eye drops and ointments possess low bioavailability and limited therapeutic outcomes due to the unique protective properties of the eye (*e.g.*, blinking reflex, nasolacrimal drainage, short precorneal residence time, and limited corneal permeability)[4]. For example, topical administration (*e.g.*, eye drops) mainly targets the anterior segment, such as the cornea and conjunctiva, but is limited by low bioavailability (less than 5%) due to anatomical barriers and tear drainage; only small volumes (a drop, about 30–50 μL) can be applied, and frequent dosing is needed, but it is non-invasive and easy for self-administration[5]. Intravitreal injections deliver drugs directly into the vitreous cavity near the retina, allowing high concentrations at the posterior segment, but require small injection volumes (0.05–0.1 mL). Intravitreal injection is invasive, and involves the risk of infection, retinal detachment, and require frequent clinical visits[6]. Periocular routes (*e.g.*, subconjunctival, sub-tenon) can target both anterior and posterior segments by placing drugs in spaces around the eye, allowing larger volumes than topical but less than intravitreal, and can bypass some

barriers, but are still invasive and may cause discomfort or hemorrhage. Systemic administration (oral or intravenous) is least effective for ocular delivery due to poor penetration into the eye and low drug accumulation in ocular tissues but can be suitable for some systemic diseases affecting the eye[7]. This necessitates repeated instillations of concentrated solutions to attain the required therapeutic effect, which reduces patient compliance.

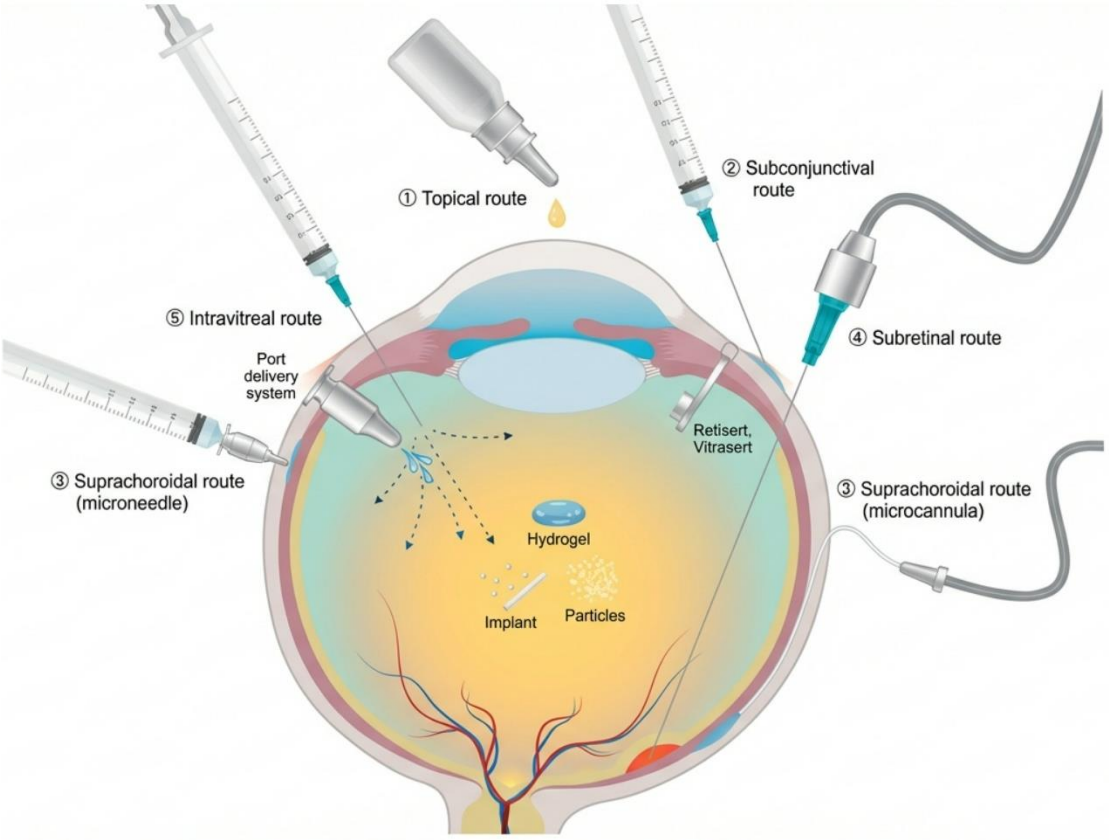

Figure 1. Examples of the commonly exploited administration routes for ocular drug delivery: (1) topical, (2) subconjunctival, (3) suprachoroidal, (4) subretinal, and (5) intravitreal injection and port delivery system. Reproduced from [3] (under the license of CC BY 4.0)

Several studies have highlighted the barriers and limitations associated with ocular drug delivery, as well as the impact of the physicochemical properties of drugs on ocular bioavailability. Invasive approaches, such as intravitreal injections, enable direct delivery of drugs to the posterior segment and achieve high intraocular concentrations but are associated with risks including infection, optic nerve damage, and poor patient compliance due to their traumatic and repetitive nature[8]. In contrast, non-invasive methods like topical eye drops are favored for their safety, ease of use, and patient compliance, yet they face ocular barriers such as the corneal epithelium, conjunctiva, sclera, tear film, and dynamic clearance mechanisms, resulting in extremely low bioavailability and limited drug penetration to the posterior segment[9]. These static and dynamic barriers, including tear turnover, nasolacrimal drainage, and blood-ocular barriers, restrict both the rate and extent of drug delivery, necessitating frequent dosing and leading to poor therapeutic outcomes and compliance[10]. Therefore, overcoming these route-specific ocular barriers remains a central challenge in the development of effective ocular drug delivery systems[11]. Advancements in nanotechnology-based drug delivery systems offer additional benefits for existing therapies.

Nanocarriers of various types, shapes, and morphologies have been exploited for diverse biomedical applications, including ocular delivery[12–16]. The morphology of nanoparticles is crucial in dictating their efficacy due to its impact on cellular binding and uptake, drug release, biodistribution, and residence time within cells[17–19]. However, due to the heterogenic nature of the body organs, tissues and cells, the concept of "one size or shape fits all" does not apply[20,21]. Nanoparticle-based formulations (*e.g.*, polymeric nanoparticles, liposomes, niosomes, *etc.*) have been developed for the treatment of various ocular diseases, including glaucoma, age-associated macular

degeneration, autoimmune uveitis, and corneal and choroidal neovascularization[4,22]. Improved therapeutic outcomes were achieved *via* enhancing residence time in the precorneal area, allowing for better drug interactions with the ocular surface and targeting ocular tissues, and providing a prolonged and controlled release of the drugs at the corneal layer[3,13,23–32]. Extensive research is being conducted at the preclinical and clinical levels for the development of therapeutics for various ocular diseases using nanosized delivery systems[33–35].

Different types of nanocarriers showed the capability to overcome ocular barriers and could deliver drugs *via* the cornea and conjunctival epithelia[36–39]. Among these nanosystems, gold nanoparticles of various morphologies have been described as potential delivery systems for managing ocular diseases, as well as for diagnostic and photothermal applications. Inspired by the significant impact of nanoparticles' shapes and morphology on their pharmacological activities in ocular applications, this review highlights the effect of the morphology of gold nanoparticles on their therapeutic outcomes, while highlighting the effect of additional parameters such as particle size, surface coating and functionalization.

2. Gold nanoparticles and the control over their shape

Substantial advancement in the ability to tailor the size, shape, and surface chemistry of gold nanomaterials allows for diverse applications (*e.g.*, optical, biological, electrical, *etc.*)[40]. Several approaches (*i.e.*, physical, chemical, biological, and electrochemical) have been described in the literature for synthesizing gold nanoparticles of various sizes and morphologies (**Figures 2 and 3**). Chemical methods, such as the Turkevich and seed-mediated methods, are frequently used for synthesizing gold nanoparticles. They usually involve two main steps, reduction and stabilization. In the Turkevich method, gold nanoparticles are synthesized by treating a chloroauric acid

solution with sodium citrate, which serves as both a reducing agent and a stabilizer, preventing the particles from aggregating. The seed growth method enables the control of particle size and geometry of gold nanoparticles by adjusting the concentrations of seeds, structure-guiding agents, and reducing agents. The physical approach utilizes radiation (*e.g.*, gamma radiation, laser ablation, and microwave) for the synthesis process and results in the development of homogenous small-sized gold nanoparticles (≤40 nm) of high purity[41]. Biological methods offer an alternative, sustainable, clean, and eco-friendly approach compared to chemical methods. This involves the use of biological systems such as bacteria, fungi, and plant extracts to synthesize gold nanoparticles with superior morphological control. Several literature reviews provide detailed procedures described for the synthesis of gold nanoparticles and tuning their morphology[40,42,43].

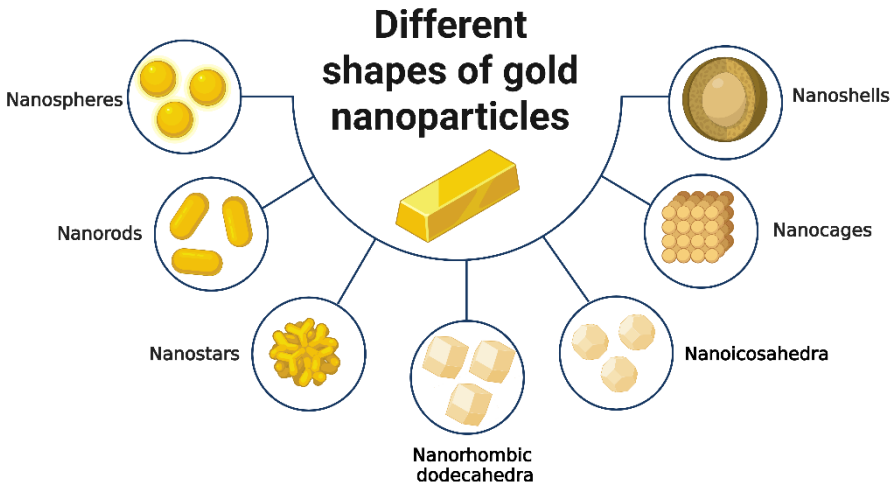

Figure 2. Different shapes of gold nanoparticles. Created by BioRender.com.

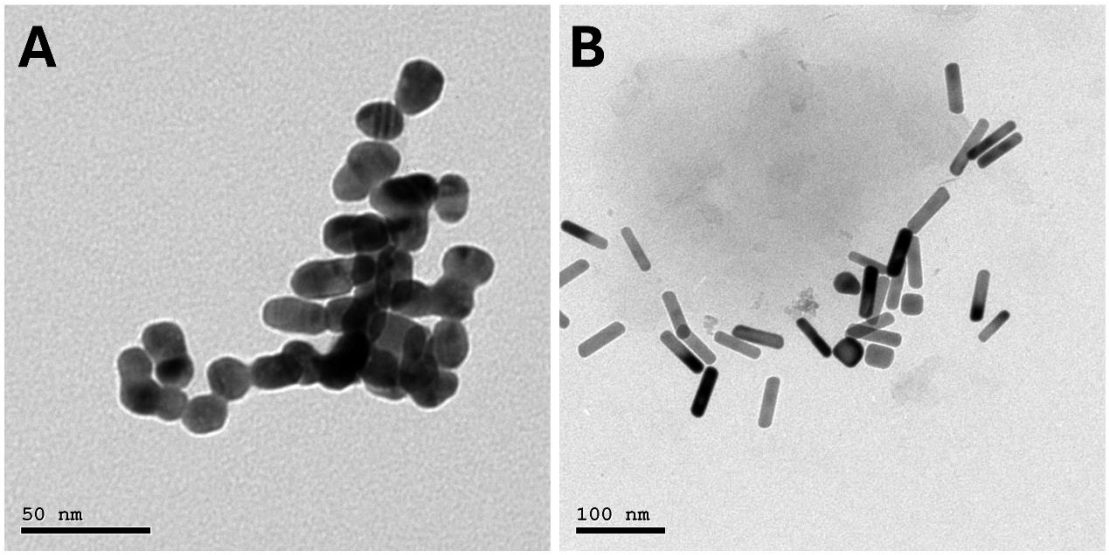

Figure 3. TEM images of gold nanoparticles. (A) Spherical nanoparticles. (B) Rod-shaped nanoparticles.

3. Gold nanoparticles of various morphologies for ocular applications

The optical properties of gold nanomaterials are significantly influenced by their size and shape (spherical, nanorods, nanostars, *etc.*). The surface plasmon resonance resulting from the precise electron cloud oscillation on the surface of gold nanomaterials is influenced by both the surrounding medium and the material's cross-section. Hence, accurate adjustment of these features enables exceptional multifunctionality in molecular diagnostics and biosensing. Given the tunability of the physicochemical characteristics of gold nanostructures and the possible modifications that can be attained by altering their structural dimensions *via* various fabrication techniques, these materials have been considered as suitable candidates for colorimetric analysis, biosensing, photothermal transduction, and imaging applications[40]. Gold nanoparticles have been exploited for diagnostic purposes and for the treatment of ocular diseases. The development of gold nanoparticles with diverse morphologies (**Figure 2**) has greatly influenced their imaging and therapeutic applications[44]. For example, tuning the shape of gold nanoparticles allows for adjusting their optical

properties, which in turn contributes to their enhanced penetration efficiency into deep eye tissues, thereby facilitating better diagnostic and theranostic outcomes. Spherical gold nanoparticles are easy to synthesize, highly biocompatible, and stable in suspension, which helps prevent agglomeration and ensures uniform cellular distribution, but their optical absorption is limited to 500–580 nm, restricting deep tissue imaging and therapy unless aggregated to shift their plasmon resonance to the NIR region[45]. Their spherical shape also enhances interaction with cellular membranes, supporting efficient uptake and even intracellular distribution, which is beneficial for therapeutic effectiveness. In contrast, non-spherical gold nanoparticles, such as nanorods and nanostars, offer tunable optical properties with plasmon resonance in the NIR region (up to 1000 nm for rods and 700–900 nm for stars), enabling deeper tissue penetration and stronger imaging contrast in ophthalmic imaging modalities like photoacoustic imaging and optical coherence tomography (OCT)[46]. Non-spherical shapes, especially nanostars, provide enhanced local electric fields and larger scattering cross-sections, resulting in superior signal enhancement for imaging and therapy (**Figure 4**)[47]. The following sections review the application of spherical and nonspherical gold nanoparticles in various ocular applications (**Table 1**).

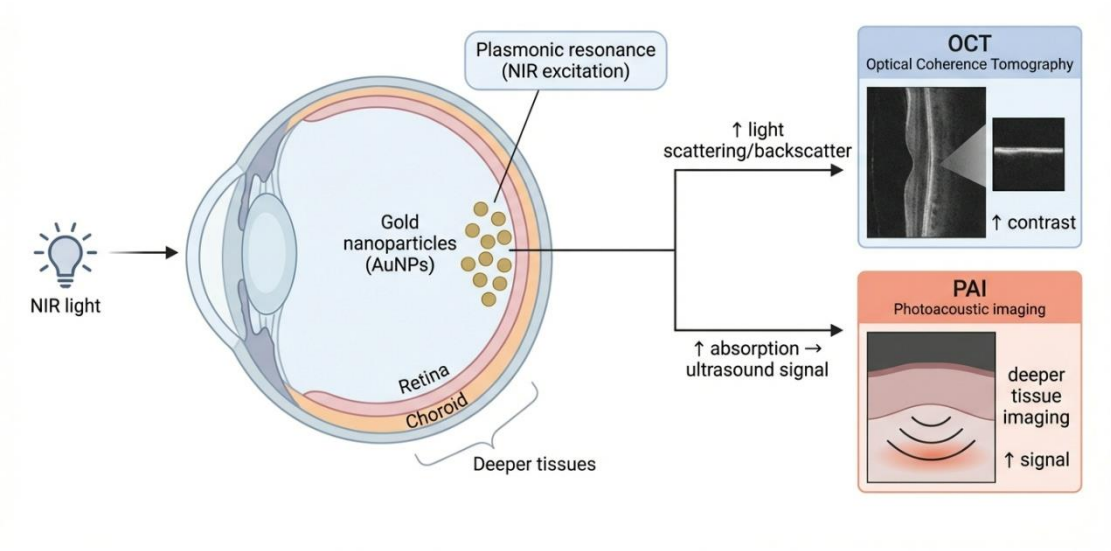

Figure 4. Schematic illustrating the use of gold nanoparticles in ocular imaging. Created by BioRender.com.

Spherical gold nanoparticles: size and surface considerations

Spherical gold nanoparticles have been commonly described in the literature for the management of ocular diseases. Surface modification and functionalization of gold nanoparticles improved their mobility and permeability across ocular barriers (**Figure 5**). For example, Apaolaza and coworkers developed gold nanoparticles as a promising delivery system for addressing ocular neovascularization and related disorders[48]. In their study, gold nanoparticles were coated with low-molecular-weight hyaluronan to enhance the permeability of the nanoparticles and to target them to CD44 receptors, which are expressed in the eye and bind to hyaluronic acid. The gold nanoparticles were prepared in different sizes (*i.e.*, 21.88 and 50.26 nm), and the size of the coated nanoparticles was almost double that of the uncoated counterparts (*i.e.*, 53.22 and 90.01 nm). During a 4-week *in vitro* study, coated gold nanoparticles demonstrated higher stability and resistance to the formation of protein corona. Moreover, despite the increase in size after coating, hyaluronic acid coating resulted in better diffusion into

the vitreous matrix and penetrating the retinal layers, that cannot be achieved by the uncoated gold nanoparticles, as confirmed by transmission electron microscopy. Coating gold nanoparticles with hyaluronic acid provides an additional benefit of CD44 targeting, an overexpressed protein in several ocular diseases[48]. The affinity of CD44 receptors for hyaluronic acid enables better cell adhesion and promotes receptor-mediated endocytosis of hyaluronic acid-conjugated drugs or delivery systems. A study by Sonntag and co-workers investigated the optimal size of gold nanoparticles for targeting the trabecular meshwork, a tissue located near the cornea responsible for the aqueous humor flow in the eye[49], to be utilized for encapsulating anti-glaucoma drugs[50]. In their study, spherical nanoparticles of different sizes (*i.e.*, 5, 60, 80, and 120 nm) were examined, either uncoated or coated with hyaluronic acid, for enhancing colloidal stability. Coating with hyaluronic acid resulted in a slight increase in particle sizes (between 2 and 14 nm), while adding superior colloidal stability compared to the uncoated counterparts. *Ex vivo* perfusion studies of porcine eyes were carried out to assess the gold content of each tissue sample of the anterior eye chamber (ciliary body, cornea, iris, lens, and trabecular meshwork) 6 h after injection of the gold nanoparticles. A large number of small gold nanoparticles (5 nm) were found in the trabecular meshwork. However, a higher gold content was observed in the case of gold nanoparticles with larger particle sizes. This was attributed to the higher volume-based accumulation in the trabecular meshwork (*i.e*, increased overall particle volume in the tissue). Hyaluronic acid-coated gold nanoparticles of larger sizes (*i.e.*, 60 and 120 nm) demonstrated an extracellular and intracellular distribution in the trabecular meshwork, as confirmed by transmission electron microscopy (**Figure 6**), with no significant differences observed for both particle sizes. The study concluded that the developed gold nanoparticles could be prepared as a depot formulation to overcome the rapid

turnover of the aqueous humor and allow for a sustained release of the loaded drug into the anterior chamber of the eye and distributed to the trabecular meshwork[50]. In an *in vivo* mouse model, topical application of hyaluronic acid-coated gold nanoparticles demonstrated significantly enhanced distribution in the posterior segment of the eye as compared to their uncoated counterparts (**Figure 7**)[51].

PEGylation of gold nanoparticles (*i.e.*, coating gold nanoparticles with polyethylene glycol (PEG)) can inhibit the nonspecific adsorption of different types of proteins (*e.g.*, proteins related to opsonization) and prolong the blood circulation time[52]. Ranibizumab biosimilar (Mab), a biosimilar of ranibizumab, a vascular endothelial growth factor (VEGF)-specific antibody fragment used as a standard therapy for the management of age-related macular degeneration, has been conjugated to pegylated gold nanoparticles. The Matrigel-based tube formation assay was used to assess the anti-angiogenic activity of the developed nanoparticles. The *in vitro* assay displayed potent inhibition of tube formation of human umbilical vein endothelial cells subjected to Mab/PEG-gold nanoparticles, compared to the pegylated gold nanoparticles, which also exhibited anti-angiogenic activity[53]. This was attributed to the possible attenuation of the VEGF-A effect due to its binding with gold nanoparticles.

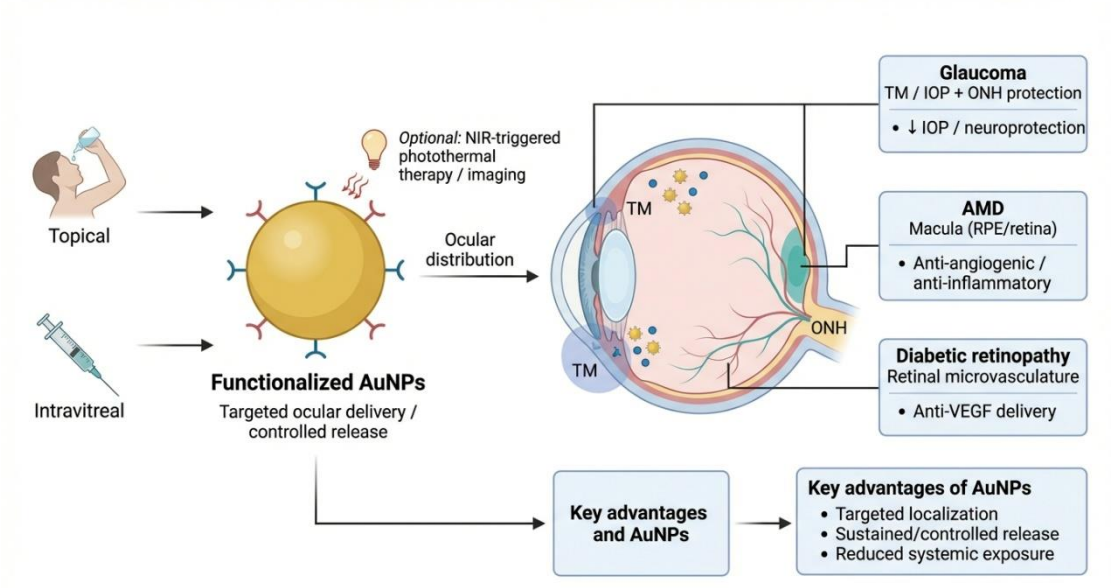

Figure 5. Schematic illustrating the targeted ocular delivery of functionalized gold nanoparticles. Created by BioRender.com.

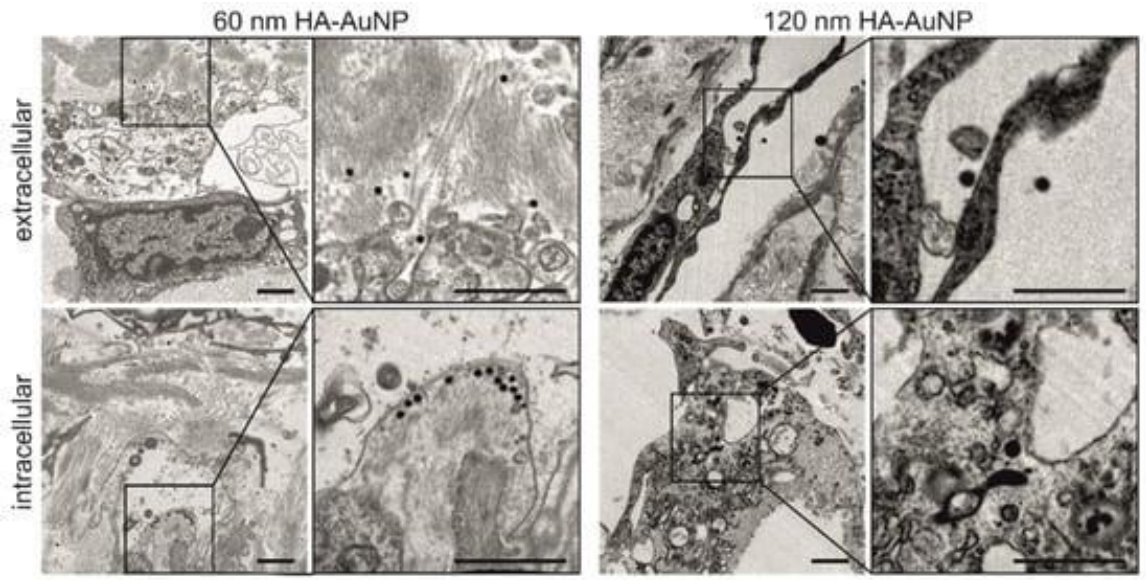

Figure 6. Distribution of gold nanoparticles within the trabecular meshwork after *ex vivo* perfusion with hyaluronic acid-coated gold nanoparticles (60 and 120 nm). Right-hand images are magnifications of the marked areas of the left-hand images; scale bars = 1 µm. Reproduced from Ref. [50] (under the license of CC BY 4.0)

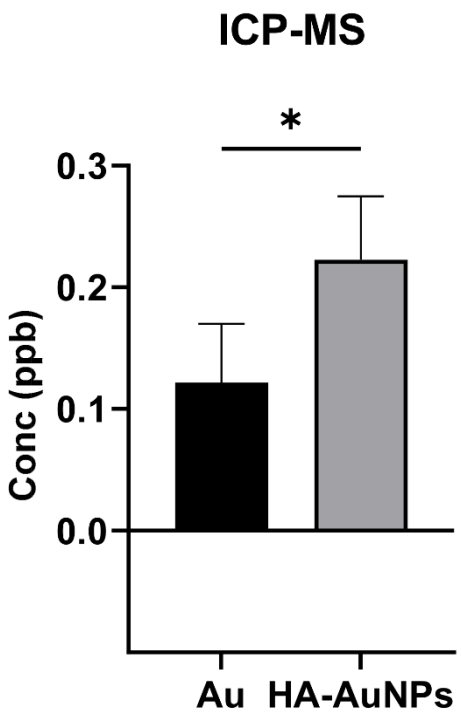

Figure 7. Inductively coupled plasma mass spectroscopy analysis in the posterior eye demonstrates enhanced distribution of coated gold nanoparticles. (* $p < 0.05$). Reproduced from Ref. [51] (under the license of CC BY 4.0).

Therapeutic contact lenses have been utilized as a strategy for ophthalmic drug delivery to overcome the limited bioavailability of traditional eye drops, while minimizing the need for frequent or high-dose administration[43,44]. The use of drug-laden contact lenses has demonstrated enhanced ocular bioavailability. Drug-laden contact lenses can be prepared using various techniques, including traditional soaking, molecular imprinting, and ion-ligand gels. These techniques aim to enhance drug loading and regulate drug release, while preserving the optical and physical properties of the lens, including transparency, contact angle, and swelling. To enhance drug loading *via* the soaking method, Maulvi et al. examined the effect of incorporating spherical gold nanoparticles into the contact lens during fabrication (gold nanoparticles-laden contact lenses) or in the drug soaking solution. Both approaches demonstrated

improved loading and uptake of timolol, an anti-glaucoma drug, into the contact lenses without altering the critical characteristics of the lens (*i.e.*, swelling and optical transparency)[54]. Although *in vitro* release profiles were not significantly improved in either approach, *in vivo* studies showed a prolonged reduction in intraocular pressure in the rabbits' eyes treated with gold nanoparticle-laden contact lenses. A higher accumulation of the drug was observed in the iris-ciliary muscle, attributed to the accumulation of gold nanoparticles inside the contact lenses, which increased drug permeability and accumulation[54]. Similarly, a study by Guo and co-authors demonstrated that gold nanoparticles-laden contact lenses enhanced ketotifen uptake from a soaking solution and exhibited enhanced *in vitro* and *in vivo* properties without altering the properties of the contact lenses[55]. Spherical gold nanoparticles were added either inside the contact lens (*i.e.*, in the lens matrix) or in the soaking solution (*i.e.*, outside the contact lens) to tackle the drawbacks of the conventional soaking method (*e.g.*, alteration of mechanical properties and ion permeability of the contact lens). The study revealed that nanoparticles loaded into the contact lens enhanced the uptake of the drug from the soaking solution compared to the traditional soaking solution and the solution containing gold nanoparticles. Moreover, lower burst release and controlled release up to 96 h were achieved in the case of gold nanoparticles loaded into a contact lens. *In vivo* studies displayed that ketotifen concentration was consistently high in the rabbit tear fluid at all measured time points compared to the soaked contact lens and the ketotifen eye drop solution. While the ketotifen eye drop solution provided a rapid initial burst release and limited drug retention that was non-detectable after 12 h, the gold nanoparticles-laden contact lens demonstrated high drug retention up to 72 h. Interestingly, no ocular irritation was reported, and histopathological studies demonstrated normal corneal histopathology during the *in vivo* study over 72 h. Worth

noting is that the gold nanoparticles-laden contact lens displayed insignificant changes in the optical transmittance as compared to the contact lens prepared by the traditional soaking method, which demonstrated a significant drop in the transmittance[55].

Gold nanoparticles have also been incorporated into other nanosystems (*e.g.*, liposomes) together with drugs as a contrasting agent for delivering drugs to the posterior segment of the eye. For example, Salem and co-authors prepared flucytosine-capped gold nanoparticles-loaded liposomes to enhance the intraocular penetration of the drug and evaluate its antifungal activity upon topical administration into the eye[56]. The developed formulations demonstrated significant *in vitro* antifungal activity against *Candida albicans* compared with the free flucytosine and gold nanoparticle solutions. Of the tested nanosystems, F6, which comprised the drug and gold nanoparticles encapsulated in phosphatidylcholine, cholesterol, Span 60, and stearylamine at a molar ratio of 1:1:1:0.15, respectively, showed the maximum mean diameter of the growth inhibition zone. The incorporation of gold nanoparticles with the drug into liposomes resulted in enhanced antifungal activity. This was attributed to the accumulation of insoluble gold in the fungal cell wall, which results in the disruption of transmembrane energy metabolism and the membrane electron transport chain[57]. Gold nanoparticles may also lead to fungal DNA mutation and dissociation of fungal enzyme complexes, which are essential for both the respiratory chain and membrane permeability. *In vivo* CT imaging in rabbits' eyes after the administration of flucytosine-capped gold nanoparticles-loaded liposomes demonstrated increased diffusion of the nanoparticles within the eyes during the six-hour study period, with the optimal formulation showing the maximum permeation distance of the nanoparticles. The optimal formulation demonstrated enhanced relative bioavailability, attributed to the increased residence time of the tested formulation, which facilitated greater flucytosine absorption. *In vivo*

studies in rabbits demonstrated the superior antifungal activity of F6 compared to the flucytosine solution, as evidenced by the healing and clearance of *Candida* keratitis in infected eyes.

Nonspherical gold nanoparticles: size and surface considerations

Nonspherical gold nanoparticles have been exploited for various applications (*e.*g., photothermal therapy, drug delivery, bio-imaging, and bio-sensing). They are increasingly explored for ocular applications due to their unique physicochemical properties (*e.g.*, exceptional optical response in the near infrared window). For example, gold nanorods have been utilized as exogenous chromophores to facilitate near infrared laser welding of ocular connective tissues[58]. Gold nanorods have been used as a self-therapeutic agent to prevent tumor growth; however, different mechanisms of action to limit angiogenesis have been reported[59,60]. Uncoated gold nanoparticles have displayed anti-angiogenic activity, evidenced by their inhibition of *in vitro* VEGF-induced endothelial cell proliferation and *in vivo* VEGF-induced angiogenesis. The suppression of angiogenesis was attributed to the binding affinity of gold nanoparticles to VEGF[61,62]. In this context, Song and co-workers synthesized gold nanodisks to evaluate their inhibitory effect on retinal neovascularization[63]. The authors fabricated gold nanodisks of various diameters and selected the 160 nm-sized nanodisks that displayed strong signals in optical coherence tomography (OCT) in a dose-dependent manner when intravitreally injected into the eyes of mice. In an *in vitro* wound healing assay, the nanodisks suppressed VEGF-induced migration of human retinal microvascular endothelial cells without inducing cytotoxicity after 48 h incubation with the highest tested concentrations. In an oxygen-induced retinopathy mouse model, intravitreal administration of the gold nanodisks (1 and 3 pM) reduced neovascularization in a dose-dependent manner without causing toxicity, as demonstrated by histological studies

(*i.e.*, unaffected integrity and absence of inflammation). The gold nanodisks were cleared entirely within 14 days, with no detectable accumulation on the inner limiting membranes[63]. In another study, PEGylated gold nanorods have also been shown to disrupt retinal angiogenesis and tumors by specifically interfering with the cytokinesis process of endothelial cells, resulting in the formation of binucleated cells that are unable to proliferate[59]. The study revealed that PEGylated gold nanorods specifically targeted the cytokinesis process of endothelial cells without causing DNA damage, cell apoptosis, and autophagy. The PEGylated gold nanorods were biocompatible and specifically disrupted the assembly of actin filaments in the contractile ring site.

Gold nanorods have also been exploited as contrast agents for photothermal optical coherence tomography (PTOCT) due to their high absorption coefficient at the wavelength used for heating by PTOCT[64,65]. In a laser-induced choroidal neovascularization (LCNV) animal model, Lapierre-Landry and co-workers studied the use of gold nanorods as contrast agents and demonstrated the ability of PTOCT imaging to detect the presence of gold nanorods in the lesion[66]. Inspired by the fact that numerous antibody-targetable surface ligands are upregulated in these laser-induced lesions (*e.g.*, ICAM2, a constitutively expressed marker on vascular endothelial cells), the same research group demonstrated the ability of PTOCT imaging of untargeted or molecularly targeted gold nanorods (ICAM2-targeted) to achieve an increased lesion-associated photothermal signal during imaging. The study revealed the detection of anti-VEGF changes in the mouse retina of an LCNV model (*i.e.*, a significant reduction in the accumulation of ICAM2-targeted gold nanorods was observed following anti-VEGF injection)[67]. This molecular information could contribute to the early detection and therapeutic intervention in patients with sight-threatening diseases.

The multimodal OCT and photoacoustic microscopy (PAM) imaging enable the early diagnosis of several ocular conditions, including wet age-related macular degeneration, characterized by the development of choroidal neovascularization (CNV), which is a type of unstructured leaky vessels. To increase the sensitivity for molecular imaging, the morphology of conventional spherical gold nanoparticles can be tuned to other morphologies, such as nanostars, which induce a red-shift in the plasmonic absorption into the near-infrared (NIR) region, thereby improving both imaging depth and contrast[68]. Nguyen and coauthors utilized gold nanostars as a molecular contrast agent for the visualization of neovascularization *via* multimodal PAM and OCT imaging[69]. In this study, gold nanostars functionalized with the arginine-glycine-aspartic acid (RGD) peptide, which binds to the integrin αvβ3 receptor overexpressed in CNV, demonstrated high photostability and no observable toxicity at the tested concentration (5 mg/mL)[69]. Owing to the red-shifted plasmonic absorption, gold nanostars significantly enhanced imaging signals by up to 17-fold in PAM and 167% in OCT—enabling clear delineation of the CNV margins from the surrounding native tissues in rabbits (**Figure 8**). Higher OCT contrast can be achieved through the modification of the size and morphology of gold nanostars (*e.g.*, increasing or reducing the number of gold nanostar branches and their aspect ratios, or increasing the core size of gold nanostars before seeding)[70]. As with gold nanostars, intravenous administration of gold nanorods functionalized with the RGD ligand into a CNV rabbit model resulted in a 27.2-fold increase in PAM and 171.4% increase in OCT owing to the strong absorption and scattering properties of the gold nanorods[71]. The use of nonspherical gold nanoparticles effectively addresses the limitation associated with the use of their spherical counterparts. Although spherical gold nanoparticles can enhance photoacoustic and OCT signals, their peak absorption wavelength overlaps with that of

hemoglobin, which limits contrast enhancement in biological tissues. Nonspherical morphologies exhibit a shifted plasmonic peak absorption from the visible to the near-infrared region. In this region, the intrinsic optical absorption from native chromophores is notably weaker, which enhances the sensitivity for molecular imaging[1]. Anisotropic gold nanoparticles are more efficient photothermal transducers for plasmonic photothermal therapy (PPTT). Although gold nanobipyramids exhibit high photothermal performance, their short-term stability, resulting from the shortening and loss of sharp tips, can have a negative impact on their plasmonic properties for PPTT[72]. Hence, surface stabilization of the gold nanobipyramids by coatings such as citrate was carried out and resulted in the development of nanoparticles that exhibited the highest temperature increase (40 °C at 2.0 W cm^{-2}) after 15 min of 808 nm NIR laser irradiation. This significant temperature rise is crucial for effective PPTT, as it can induce the desired therapeutic effects without damaging surrounding tissues as predicted by *in vitro* cytotoxicity studies (*i.e.*, the nanoparticles are biocompatible with major corneal cell types: human corneal endothelial cells, human corneal fibroblasts, and corneal epithelial cells)[72].

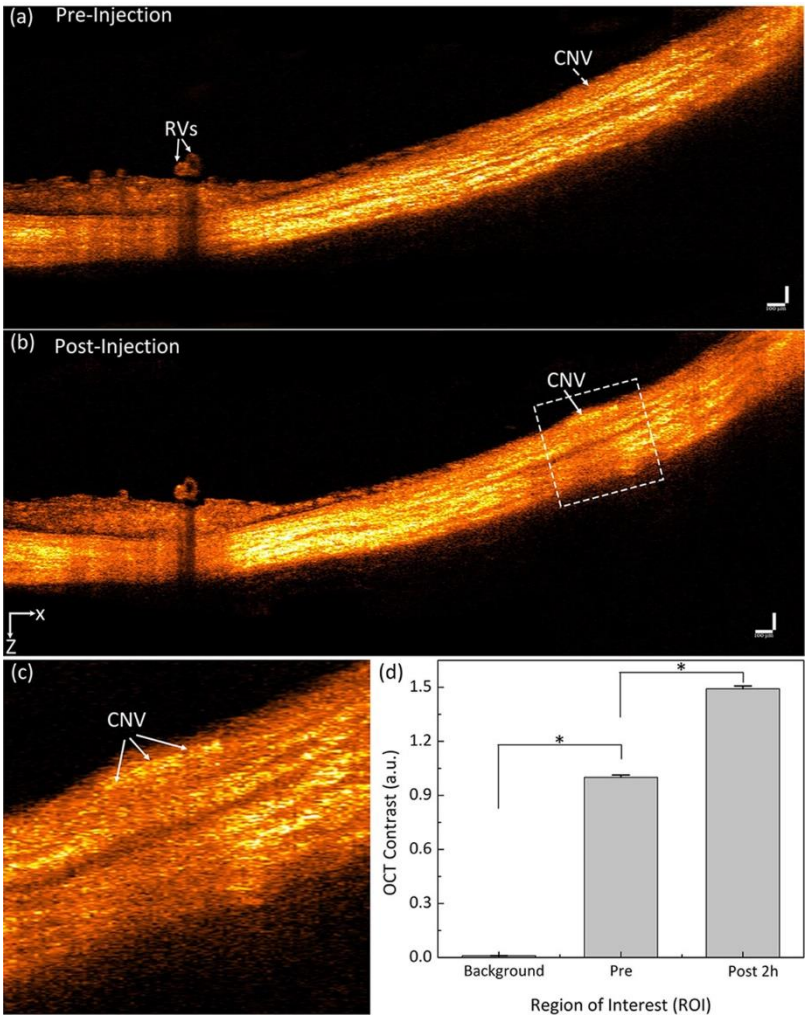

Figure 8. Enhanced *in vivo* OCT imaging contrast using gold nanostars: (a-b) B-scan OCT images before and two h after intravenous gold nanostars injection. White arrows indicate CNV position. (c) Magnified view of the area outlined in (b). (d) Spectral analysis of OCT intensity within the CNV before and two h after gold nanostars administration. Reproduced with permission from Ref. [69].

Despite extensive studies exploring how size, shape, aspect ratio, and surface chemistry influence pharmacokinetics, biodistribution, cellular uptake, and therapeutic efficacy in general biomedical applications[73–77],comparative studies evaluating the effect of nanoparticle morphology on ocular drug delivery remain limited. Among the physicochemical properties, the shape and morphology displayed significant effects on

cellular binding, uptake and pharmacological activities[78–85].To date, only a few studies have directly investigated and compared the influence of gold nanoparticles' morphology on ocular therapy. In our previous work, we compared spherical and rod-shaped gold nanoparticles loaded with a carbonic anhydrase inhibitor for glaucoma management[78]. Spherical nanogolds displayed superior efficacy in lowering intraocular pressure compared to the rod-shaped counterparts in a glaucoma rabbit model that was attributed to the enhanced ocular retention of spherical drug-loaded gold nanoparticles within collagen fibers of the stroma, as confirmed by TEM imaging. Eye irritation test displayed excellent ocular tolerance in case of the drug loaded-gold nanospheres. The rod-shaped counterpart showed signs of irritation on the cornea, conjunctiva, and iris that might be attributed to the presence of the cationic CTAB during the synthesis of gold nanorods that allows for the axial growth of the rod[78,86]. Normal microscopic configuration of the cornea and retina, with no evidence of inflammation or tissue abnormalities was observed in case of the spherical gold nanoparticles, while tissue abnormalities were observed in the eyes of rabbits treated with the rod-shaped counterparts.

Although ocular-focused studies are rare, insights from non-ocular applications suggest that nanoparticle morphology strongly influences therapeutic performance. For example, in photothermal therapy, Yang and co-workers investigated gold nanoparticles of three morphologies (nanospheres, nanorods and nanostars) possessing similar surface modification[87]. While all gold nanoparticles displayed photothermal therapeutic effect and were able to convert 808 nm near-infrared laser light energy into heat through *via* localized surface plasmon resonance, gold nanostars demonstrated superior photothermal and antitumor activity, likely due to their larger surface area providing space for more plasma to resonate with the near-infrared light and to trap

more induced electrons on the surface[87]. Similarly, Pakravan and co-authors displayed that gold nanostars exhibited lower cytotoxicity, highest cellular uptake and highest heat generation as compared to gold nanoparticles of hollow, rods, cages, spheres, Fe-gold and Si-gold core shells morphologies. Upon photothermal treatment, gold nanostars displayed enhanced apoptosis induction rate in MCF-7 cells due to significant heat production [88]. Functionalization of spherical gold nanoparticles with dyes (infrared 808 dyes) enhanced photothermal conversion efficiency by a factor of 4 as compared to unmodified gold nanoparticles of similar particle size[89].

Nanoparticles with rough surface topology could provide more contact points on the cell membrane and hence increase the interaction ability, resulting in improved cellular internalization. For example, gold nanoparticles possessing urchin-like morphologies of various Feret lengths and surface topographies have been designed as an ocular delivery vehicle for managing dry eye disease[90]. The rough-surfaced urchin-like morphologies exhibited enhanced cytoadhesion and bioadhesion, particularly in case of longer branches, and hence significantly increasing the corneal retention time by 150-fold at 7 days post-instillation compared with smooth gold nanoparticles.

Taken together, these findings indicate that gold nanoparticles' morphology is a critical determinant of therapeutic efficacy, and further systematic studies are needed to optimize nanoparticle design for ophthalmic applications.

Table 1. Gold nanoparticles for ocular applications. TEM: transmission electron microscopy, DLS: dynamic light scattering.

	Composition	Size of gold nanoparticles	Remarks	Advantages	References
Spherical gold nanoparticles	Hyaluronan-coated gold nanoparticles	- Uncoated (21.88 ± 0.98 and 50.26 ± 1.78 nm) - Coated (53.22 ± 3.36 and 90.01 ± 2.58 nm)	- Coated gold nanoparticles demonstrated higher stability and resistance to the formation of protein corona. - Coating with hylauronic acid enhanced stability, facilitated diffusion across cell membranes and tissues, and enabled targeting through specific CD44 receptor interaction. - *Ex vivo*, the ability of coated gold nanoparticles to diffuse through the vitreous humour and their affinity to reach the deeper retinal layers indicate their potential for the treatment of intraocular vascular diseases.	Enhanced stability, targeted delivery *via* CD44 receptor binding, and improved diffusion across ocular barriers	48
	Hyaluronic acid-coated gold nanoparticles	15-20 nm	- In an *in vivo* mouse model, topical application of hyaluronic acid-coated gold nanoparticles demonstrated greater distribution in the posterior eye segment (retinal layers) as compared to uncoated ones. - .	Non-toxicity, efficient biodistribution, and active site-specific targeting via hyaluronic acid-CD44 affinity	51
	Ranibizumab biosimilar/PEG-conjugated gold nanoparticles (MPGs)	- Core size (≈ 5 nm) - 5 K- and 10 K- MPGs were ≈ 20 and 30 nm, respectively)	- MPGs showed a potent antiangiogenic effect that was comparable to that of the Mab solution. - PEG-gold nanoparticles also demonstrated anti-angiogenic activity.	Potent angiogenic activity; no effect on cell proliferation in human endothelial cells	53
	Gold nanoparticles-laden contact lens loaded with timolol, an anti-glaucoma drug	65 ± 5nm	- *In vivo* studies displayed prolonged reduction in the intraocular pressure in the rabbits' eyes treated with the gold nanoparticle-laden contact lenses. -	Gold nanoparticles enhanced the uptake of timolol from the drug soaking solution to treat	54

				glaucoma without altering the critical properties of the contact lens.	
	Flucytosine capped with gold nanoparticles-loaded liposomes	Optimal formulation F6 135.1 ± 12.0 nm	- The optimal formulation demonstrated significant *in vitro* antifungal activity against *Candida albicans* compared with the free flucytosine and gold nanoparticles solutions. - *In vivo* CT imaging in rabbits' eyes following the administration of F6 demonstrated the highest penetration of the gold nanoparticles within the eyes during the six hours of study. - F6 showed enhanced relative bioavailability that was attributed to the improved residence time of the tested formulation, allowing for greater flucytosine absorption. - *In vivo* studies in rabbits demonstrated superior antifungal activity of F6 as compared to the flucytosine solution evidenced by the healing and disappearance of *Candida* keratitis of infected eyes.	Enhanced antifungal activity, increased ocular penetration, improved bioavailability.	56
Nonspherical gold nanoparticles	Gold nanodisks	Diameter of 160 nm	- In an *in vitro* wound healing assay, the nanodisks suppressed VEGF-induced migration of human retinal microvascular endothelial cells without causing cytotoxicity after 48 h incubation with the highest tested concentrations. - In an oxygen-induced retinopathy mouse model, intravitreal administration of the gold nanodisks (1 and 3 pM) demonstrated a dose-dependent reduction in neovascularization without causing toxicity as confirmed by histological studies.	No evidence of toxicity in retinal integrity and function.	63

Pegylated gold nanorods	Length = 77.5 ± 6.5 nm Width = 15.5 ± 1.1 nm Aspect ratio of about 4.9	- PEGylated gold nanorods specifically targeted the cytokinesis process of endothelial cells without inducing DNA damage, cell apoptosis, and autophagy. - Pegylated gold nanorods can be used to interfere with retinal angiogenesis and tumors.	Effective at targeting endothelial cell processes, no apparent DNA damage, no apparent retinal toxicity.	[59]
Molecularly targeted gold nanorods (ICAM2-targeted)	Dimensions of 10 nm × 35 nm	- PTOCT imaging of molecularly targeted gold nanorods allowed for the detection of anti-VEGF-induced changes in the mouse retina in an LCNV model.	Enhanced imaging sensitivity.	[67]
Gold nanostars functionalized with RGD peptide	30 nm	- *In vivo*, gold nanostars significantly enhanced imaging signals—by up to 17-fold in PAM and 167% in OCT—enabling clear delineation of the choroidal neovascularization margins from the surrounding native tissues.	High photostability, enhanced imaging contrast (PAM, OCT), RGD peptide bind integrin αvβ3 which is over-expressed choroidal neovascularization, non-toxic at the tested concentrations.	[69]
Gold nanorods functionalized with the RGD ligand	- Width = 34.17 ± 4.85 nm and length =103.28 ± 12.07 nm (TEM) - 113 nm (DLS)	- *In vivo*, intravenous administration of RGD functionalized-gold nanorods into a choroidal neovascularization rabbit model resulted in a 27.2-fold increase in PAM and 171.4% increase in OCT.	Enhanced imaging and visualization in vivo without tissue destruction.	[71]

4. Conclusion and perspectives

Advanced design and synthesis of nanomaterials have contributed to early detection and better management of ocular diseases. Gold nanoparticles of varying shapes and sizes have been employed in ophthalmology for diagnostic and therapeutic purposes (**Figure 9**). One of the key features of gold nanoparticles is the precise control over their synthesis, which enables the fine-tuning of particle size, shape, and surface chemistry. These morphological properties play a crucial role in dictating the cellular uptake, penetration, and biodistribution of gold nanoparticles within ocular tissues. For instance, spherical gold nanoparticles, especially smaller particles, demonstrate enhanced tissue penetration and have been mainly described for the management of ocular neovascularization and related disorders. In addition to possible surface functionalization, the ability to improve drug stability and delivery positions them as a valuable tool in the advancement of treatment strategies. While spherical gold nanoparticles are used to enhance imaging modalities such as photoacoustic imaging and OCT due to their pronounced localized surface plasmon resonance in the visible spectrum, their peak optical absorption typically lies within the 500–550 nm range, which significantly overlaps with the peak absorption of endogenous chromophores, particularly hemoglobin. Imaging contrast is often limited, especially in deeper tissues, due to elevated background signals and restricted light penetration. Anisotropic shapes (e.g., rods, cages, or stars) can offer noticeable benefits in imaging and photothermal applications. These anisotropic shapes exhibit tunable plasmonic resonance peaks that can be red-shifted into NIR region (typically 650–900 nm or even beyond). This spectral window is characterized by minimal absorption and scattering from native tissue components, which allows for superior imaging depth and contrast in photoacoustic and OCT applications. Rough-surfaced topology (e.g., urchin-like gold

nanoparticles) can also enhance cellular adhesion and hence corneal residence time, allowing for improved cellular internalization. This tunability, together with enhanced functional performance, makes nonspherical gold nanoparticles an attractive tool for targeted molecular imaging, image-guided therapy, and real-time diagnostics, particularly in applications that require deep tissue penetration (*e.g.*, tumor detection, vascular imaging, and monitoring of inflammation).

A number of clinical trials are reported for gold nanoparticle platforms, however none of these are for ocular applications. A better understanding of the behavior of gold nanoparticles in the ocular environment, along with the influence of their morphology on their pharmacological activities, facilitates significant advancements in tuning the structures and morphologies of nanomaterials to achieve improved therapeutic outcomes and overcome current limitations. The safety, scale-up, and reproducibility of therapeutic and diagnostic gold nanoparticles are crucial parameters to be considered for commercialization. Although several studies reported the use of gold nanoparticles as contrast agents for OCT imaging in the eye, further studies are required to ensure their safety. Detailed biocompatibility and toxicity studies are needed prior to clinical applications. *In vivo* tracking, long-term accumulation and safety studies, as well as clearance pathways and retinal toxicity risks are also important aspects towards the development of next generation nanotherapeutics and diagnostics for eye diseases.

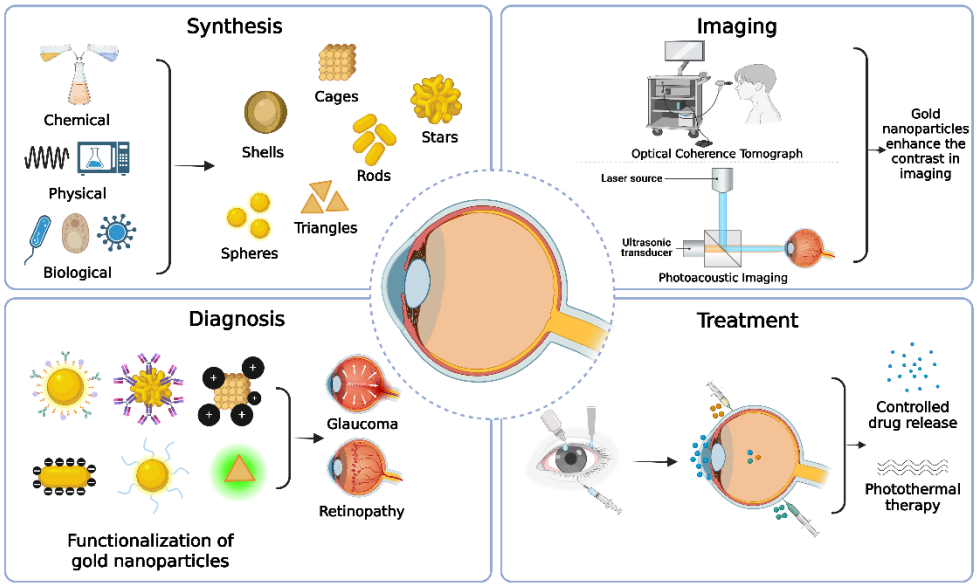

Figure 9. Gold nanoparticles of various shapes and sizes are exploited for multiple ocular applications. Created by BioRender.com.

List of Abbreviations

PEG	Polyethylene glycol
VEGF	Vascular endothelial growth factor
OCT	Optical coherence tomography
PTOCT	Photothermal optical coherence tomography
LCNV	Laser-induced choroidal neovascularization
PAM	Photoacoustic microscopy
CNV	Choroidal neovascularization
NIR	Near-infrared
RGD	Arginine-glycine-aspartic acid
PPTT	Plasmonic photothermal therapy
TEM	Transmission electron microscopy
DLS	Dynamic light scattering

Author contributions statement

Conceptualization: M.E.; writing—original draft preparation: E.B.A., M.A.M., S.M.H., N.O.A., R.I., N.S.N., R.A.E, N.G.E.; writing—review and editing: N.G.E., M.E.; visualization: E.B.A.; supervision: M.E. All authors have read and agreed to the published version of the manuscript.

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