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Beyond the injection: delivery systems reshaping retinal disease management

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Abstract

Introduction: Intravitreal injections remain the standard for treating common retinal diseases including age-related macular degeneration (AMD), diabetic macular edema (DME) and diabetic retinopathy. However, frequent administration creates significant treatment burden due to limited drug half-life and the chronic nature of these conditions.

Areas covered: This review summarizes emerging drug delivery techniques and therapies for retinal disease that have achieved FDA approval within the past five years or have advanced to Phase 3 development, including intravitreal sustained-release platforms and alternative delivery routes (suprachoroidal, subretinal, topical, and subcutaneous). Specific innovations discussed include the ranibizumab port delivery system, EYP-1901 (Duravyu, vorolanib implant), KSI-301 (tarcocimab tedromer), KSI-501, OTX-TKI (Axpaxli, axitinib implant), 4D–150, revakinagene taroretcel-lwey (Encelto, NT-501, encapsulated cell therapy), Xipere (triamcinolone acetonide injectable suspension), AU-011 (belzupacap sarotalocan targeted delivery), ABBV-RGX-314, elamipretide, and OCS-01 (high concentration dexamethasone).

Expert opinion: Promising innovations include sustained-release intravitreal implants, topical and subcutaneous delivery systems, and targeted methods like suprachoroidal and subretinal injections, each with unique advantages and limitations. Challenges include overcoming the blood-retinal barrier, surgical complications with implantable devices, and ensuring patient adherence. Advances in smart delivery systems, drug formulations, and predictive models, alongside interdisciplinary collaboration, will be crucial in achieving personalized, effective, and sustainable retinal therapies.

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Declarations of interest

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1. Introduction

Common retinal pathologies, including age-related macular degeneration (AMD), diabetic retinopathy (DR), diabetic macular edema (DME), and retinal vein occlusion (RVO) require timely and repetitive intervention to prevent permanent vision loss. Drug delivery to the posterior segment of the eye is complex due to the eye's unique biochemical, physiological and anatomical characteristics, including the blood-retinal barrier. Intravitreal injection of medications, in particular anti-vascular endothelial growth factor (VEGF) agents, has become the standard of care over the past decade for treating these common retinal pathologies. Intravitreal injection techniques allow for the delivery of a relatively high concentration of drug to the target tissue with a small risk of complications such as endophthalmitis, retinal detachment, or cataract formation. Intravitreal injection therapies are limited; however, as they are highly invasive, costly and have a short duration of action requiring frequent administration. Favorable long-term visual outcomes that mirror clinical trial results have been demonstrated in real-world studies in AMD patients who receive fixed intravitreal injections dosing with over 10 injections per year [1], while other studies suggest that patients receiving fewer than six intravitreal injections annually experience less visual acuity gains [2–5]. Monthly or bimonthly anti-VEGF therapy presents significant time and cost burden due to the chronic nature of retinal disease and limited medication half-life. To address these significant treatment burdens, innovative therapies are being developed using novel drug delivery techniques including sustained-release devices, intravitreal reservoirs, hydrogels, suprachoroidal and subretinal delivery and topical and systemic pharmacologic administration (Figure 1).

This article explores the emerging drug delivery techniques and therapies for retinal disease and their transformative potential in patient care. For the purposes of this review, we define 'drug delivery systems' as technologies or methodologies that transport therapeutic agents to their target sites within the eye, with specific focus on approaches that modify release kinetics, enhance target specificity, or utilize novel anatomical routes to overcome barriers to drug delivery in the posterior segment. To maintain a clear scope, only therapies approved by the United States Food and Drug Administration (FDA) within the past five years or currently in at least Phase 3 of development will be cited as examples, despite the breadth of novel treatments currently in clinical development.

2. Intravitreal delivery

The intravitreal space remains the most employed route for the delivery of therapeutic agents for common retinal diseases due to its high safety, minimum invasiveness, convenient application, and efficacy [7]. Currently, the FDA has approved five anti-VEGF medications for use intravitreally: pegaptanib sodium (Macugen, OSI Pharmaceuticals, Long Island, NY, U.S.A.), ranibizumab (Lucentis, Genentech, San Francisco, CA, U.S.A.), aflibercept (Eylea,

Regeneron Pharmaceuticals, Tarrytown, NY, U.S.A.), brolucizumab (Beovu, Novartis Pharmaceuticals, East Hanover, NJ, U.S.A.), and faricimab (Vabysmo, Genentech, San Francisco, CA, U.S.A.). Aflibercept has been approved in both a 2 mg/0.05 mL dose (Eylea) and high-dose 8 mg/0.07 mL dose (Eylea HD). Bevacizumab (Avastin, Genentech, San Francisco, CA, U.S.A.) is another anti-VEGF agent whose off-label use is widespread among retina specialists. It is important to note that pegaptanib sodium was eventually discontinued in lieu of more effective anti-VEGF agents. Furthermore, in recent times, there has been an increase in the development of anti-VEGF biosimilar therapies as a more cost-effective, clinically equivalent alternative to the branded agents referenced above. For instance, ranibizumab-nuna (Byooviz), launched in partnership between Samsung Bioepis (Incheon, South Korea) and Biogen (Cambridge, MA, U.S.A.), was the first ophthalmology and ranibizumab biosimilar approved by the FDA in September 2021 with an average difference in sale price of 31.3% compared to ranibizumab [8]. Since then, several biosimilars have been approved in the United States, including ranibizumab-eqrn (Cimerli, Coherus BioSciences, Redwood City, CA, U.S.A.), aflibercept-jbvf (Yesafili, Biocon Biologics, Bengaluru, India), aflibercept-yszy (Opuviz, Samsung Bioepis, Incheon, Republic of Korea), and aflibercept-mrbb (Ahzantive, Formycon AG, Martinsried, Germany) [8–10].

Despite the efficacy of these agents, they remain limited by their relatively short half-lives. In human nonvitrectomized eyes, the intraocular half-life has been estimated between 7.3 and 9.1 days for aflibercept, 7.2 days for ranibizumab, and between 4.9 and 9.8 days for bevacizumab [11–14]. Thereby, these medications require intravitreal injections monthly, bimonthly or at a minimum every three months (brolucizumab) to maintain their efficacy [15]. This need for frequent intravitreal injections imposes a significant burden on patients and the healthcare system, which can, in turn, lead to poor adherence, follow-up and worse outcomes [16]. The growing aging population across the developed world is creating an urgent need for more accessible, cost effective, and durable long-term solutions to treat retinal pathologies [17].

Two current modalities that are being utilized to reduce the high treatment burden of frequent intravitreal anti-VEGF injections include high molar concentration therapies and multitargeted treatments. Brolucizumab is a humanized single-chain variable fragment antibody that specifically targets VEGF-A isoforms and was approved by the FDA for nAMD and DME in October 2019 and June 2022, respectively. Its unique design, with a low molecular weight of 26 kDa and high stability, allows for a higher concentration of active drug in the standard 0.05 mL injection volume. A comparative pharmacokinetic study found a significantly higher mean aqueous half-life of 9.00 days for brolucizumab compared to 2.88 days for aflibercept [18]. Brolucizumab distinguished itself as the first anti-VEGF therapy to achieve improved fluid resolution and enable extended three-month dosing after an initial loading phase, as demonstrated in the Phase 3 HAWK (NCT02307682) and HARRIER (NCT02434328) trials [19,20]. Real-world studies also highlight its effectiveness in extending treatment intervals after switching from other anti-VEGF agents [15]. However, rare but potentially serious safety concerns such as retinal vascular occlusion, retinal vasculitis, and intraocular inflammation (IOI) have limited its widespread adoption [21,22]. The MERLIN Phase 3 trial (NCT03710564), which investigated the use of brolucizumab

in refractory nAMD, was terminated due to an increased incidence of these adverse events [23].

Aflibercept, a neutralizes VEGF-A and placental growth factor (PlGF), both critical to angiogenesis. Initially approved in 2011 for nAMD at a dose of 2 mg/0.05 mL, aflibercept achieved significant clinical efficacy in the VIEW1 (NCT00509795) and VIEW2 (NCT00637377) trials with an eight-week dosing schedule after three initial monthly doses [24]. Enhanced anatomic outcomes with a 4 mg dose were noted in the Phase 2 CLEAR-IT 2 trial (NCT00320788) [25]. In August 2023, aflibercept 8 mg/0.07 mL (Eylea HD) received FDA approval for nAMD, DME, and DR following the 48-week results of the Phase 3 PULSAR (NCT04423718) and PHOTON (NCT04429503) trials, which demonstrated non-inferiority and equivalent vision gains with 12- and 16-week dosing intervals compared to bimonthly aflibercept 2 mg [26]. As aflibercept 8 mg enters clinical use, ongoing real-world studies will be essential in evaluating its safety, efficacy, and long-term durability.

Faricimab, the first and only bispecific antibody currently approved by the FDA, may represent the beginning of multitargeted treatment strategies providing more durable solutions against various retinal pathologies. Designed using CrossMAb technology, faricimab is administered intravitreally with the capability of binding to both the VEGF and Ang-2 pathways involved in the neovascularization observed in nAMD, DME, and RVO [27]. One study found an estimated intravitreal half-life of 7.5 days [28]. In the Phase 3 YOSEMITE (NCT03622580) and RHINE (NCT03622593) trials for DME, TENAYA (NCT03823287) and LUCERNE (NCT03823300) trials for nAMD, and COMINO (NCT04740931) and BALATON (NCT04740905) trials for macular edema secondary to branch (BALATON) or central or hemiretinal (COMINO) RVO, faricimab at less frequent dosing of up to 16 weeks demonstrated non-inferior vision gains and comparable central subfield thickness (CST) reductions compared to aflibercept [29–33]. Initial real-world results seem promising at the time [34,35]. However, further long-term data will help elucidate the safety, efficacy, and durability of faricimab in nAMD, DME, and RVO.

In addition to multitargeted approaches, novel intravitreal anti-VEGF agents in development also aim to address the challenges of reduced efficacy or resistance to anti-VEGF-A monotherapy by targeting other members of the VEGF family including VEGF-C and VEGF-D. An example of this is OPT-302 (sozinibercept, Opthea Limited, Victoria, Australia), which is a recombinant fusion protein ‘trap’ molecule composed of three extracellular ligand-binding domains of human VEGFR3 fused to human immunoglobin G1 constant domain (hIgG1 Fc). This molecule binds to and sequesters VEGF-C and VEGF-D, preventing ligand binding to VEGFR2 and VEGFR3 [36]. OPT-302 was intended to be administered in tandem with traditional anti-VEGF agents that target VEGF-A and thus has been the focus of many clinical trials. In a Phase 2b clinical trial (NCT03345082), patients receiving a combination of 2 mg of OPT-302 with 0.5 mg of ranibizumab achieved substantial increases in BCVA gains compared to those receiving monthly ranibizumab monotherapy at 24 weeks (+ 14.2 ± 11.61 versus + 10.8 ± 11.52 letters; $p = 0.01$). OPT-302 also produced anatomic improvements in CST compared with sham while displaying no significant differences in adverse events (AE) across groups [36]. The Phase 3 COAST

(NCT04757636) and ShORe (NCT04757610) studies are currently underway to investigate the efficacy and safety of intravitreal 2 mg OPT-302 in combination with aflibercept and ranibizumab, respectively [37].

2.1. Reservoirs for intravitreal delivery

Long-acting reservoirs for intravitreal injections drug delivery have been proposed as an alternative strategy to minimize the treatment burden from frequent anti-VEGF injections and potentially improve efficacy. The port delivery system (PDS) with ranibizumab (Susvimo, Genentech, San Francisco, CA, U.S.A.) is a noteworthy example of this approach. This device is a nondegradable, refillable implant that is surgically placed in the pars plana and allows for a sustained release of ranibizumab into the vitreous [38]. At a dose of 100 mg/mL, the PDS demonstrated mean release rates of 16.69 μg/day and 4.16 μg/day at day 3.5 and month 6, respectively [39]. Furthermore, the estimated half-life of ranibizumab release from the PDS was approximately 106 days [40]. The safety and efficacy of the PDS have been evaluated in the Phase 3 Archway trial (NCT03677934) for nAMD [41], Phase 3 Pagoda trial (NCT04108156) for DME [42], and Phase 3 Pavilion trial for DR (NCT04503551) [43], which all showed comparable results to monthly or as needed ranibizumab injections for at least one year. The ranibizumab PDS was approved by the FDA in 2021 for the treatment of nAMD, with refills anticipated every 24 weeks.

There is a black box warning; however, for an elevated risk of endophthalmitis that has been associated with this device compared to intravitreal injections. In the Archway study, 1.6% of the total 248 participants experienced endophthalmitis. Other adverse events that were noted in this trial include retinal detachment (0.8%), vitreous hemorrhage (5.2%), conjunctival erosion (2.4%), and conjunctival retraction (2.0%) [41]. It must be noted that many of these adverse events were related to improper surgical technique and thus could improve as the implantation procedure continues to evolve. In October 2022, Genentech declared a voluntary recall of the ranibizumab PDS and temporarily halted new implantations due to reported incidents of septum dislodgement [44]. Genentech has since updated the ocular implant and refill needle, reintroduced the device to market for nAMD, and gained FDA approval for DME based on positive one-year results from the Pagoda study [45]. Results of the Pagoda trial found the PDS with fixed refill-exchanges every six months met its primary endpoints of noninferiority to monthly ranibizumab in BCVA change from baseline, and that improvements in visual gains were maintained at one year [46,47]. Furthermore, approximately 95% of individuals did not need additional treatment with supplemental injections. Results of the Pavilion trial found the PDS with fixed refill-exchanges every nine months maintained diabetic retinopathy severity score (DRSS) improvements seen at one year, and that 80% of eyes achieved a two-step or greater improvement on the DRSS from pre-implant baseline at week 100 [46,47]. Furthermore, approximately 98% of participants did not need additional treatment with supplemental injections. The effect of the PDS 100 mg/mL refilled every 24 weeks on the change in corneal endothelial cell density, as measured by specular microscopy, is also being evaluated in the Phase 3 Belvedere trial (NCT04853251) [48].

2.2. Polymer-based delivery

To mitigate the treatment burden in various retinal disorders, current research in ocular drug delivery has been increasingly directed toward utilizing polymeric biomaterials. These polymers can be biodegradable or nonbiodegradable in nature and provide adaptable chemical and physical characteristics that can enhance drug solubility, regulate release rates, and improve drug retention in target tissues [49]. Synthetic polymers that are approved by the FDA and currently employed for ocular use include polyethylene glycol (PEG), polyvinyl alcohol (PVA), polyglycolic acid (PGA), polylactic-co-glycolic acid (PLGA), poly2-(dimethylamino)ethyl methacrylate (DMAEM), polycaprolactone (PCL), polyacrylic acid (PAA), and polyamidoamine (PAMAM) [50].

PLGA is a biodegradable, sustained-release polymer that has historically been a well-suited material in medicine due to its physical properties in solubility, mechanical strength, and degradation rate. Ozurdex (Allergan, Dublin, Ireland), is the representative example of such a design. Approved by the FDA in 2009 for treating posterior uveitis and macular edema secondary to retinal vein occlusion and eventually DME in 2014, Ozurdex is an erodible, PLGA-based intravitreal implant that delivers dexamethasone over a span of four to six months and undergoes complete in vivo degradation [51]. The efficacy and safety profile of Ozurdex has been substantiated in real-world settings through multiple studies [52–54].

Vitrasert (ganciclovir 4.5 mg, Bausch & Lomb, Rochester, NY, U.S.A.) was the first nonbiodegradable implant approved for retinal diseases by the FDA in 1996. It was comprised of ethylene-vinyl acetate (EVA) coated with polyvinylalcohol (PVA) that was secured to the sclera and allowed for sustained delivery of ganciclovir for a period of four to five months [55]. Despite its discontinuation, the non-erodible Durasert platform has been the catalyst for many FDA approved therapies including Retisert (fluocinolone acetonide 0.59 mg, Bausch & Lomb, Rochester, NY, U.S.A.) for uveitis in 2005, Iluvien (fluocinolone acetonide 0.19 mg, Alimera Sciences, Alpharetta, GA, U.S.A.) for DME in 2014, and Yutiq (fluocinolone acetonide 0.18 mg, Alimera Sciences, Alpharetta, GA, U.S.A.) for uveitis in 2018 [56–58]. The Iluvien intravitreal implant is also currently undergoing investigation in the Phase 4 NEW DAY trial (NCT04469595) to assess its efficacy as a baseline therapy in the treatment of center-involving DME [59].

EYP-1901 (Duravyu, EyePoint Pharmaceuticals, Watertown, MA, U.S.A.) is a sustained drug delivery technology containing vorolanib, a tyrosine kinase inhibitor (TKI), that utilizes the Durasert E™ platform. Vorolanib has binding affinity to all three VEGF receptors (VEGFRs) (VEGFR1, VEGFR2, VEGFR3), thereby proficiently inhibiting all VEGF activity within the specified tissue [60]. The Phase 2 DAVIO 2 trial (NCT05381948) for EYP-1901 demonstrated non-inferior BCVA at six months compared to bimonthly aflibercept injections in patients with nAMD. It was also reported that 85% of participants had a mean reduction in anti-VEGF injection rate compared with the six months prior to randomization, and almost two-thirds of patients did not require additional anti-VEGF injections for up to six months, illustrating the product's ability to reduce treatment burden [61]. The Phase 3 LUGANO (NCT06668064) and LUCIA (NCT06683742) trials are designed for potential global regulatory approval for every six-month re-dosing of

EYP-1901 2.7 mg in nAMD. EyePoint Pharmaceuticals recently announced the first patients were dosed in the pivotal LUGANO and LUCIA trials [62,63].

KSI-301 (tarcocimab tedromer, Kodiak Sciences, Palo Alto, CA, U.S.A.) is a humanized anti-VEGF monoclonal antibody capable of blocking all VEGF-1 isoforms that is conjugated to a high molecular weight phosphorylcholine-based biopolymer. The larger molecular structure enhances its intraocular stability and intravitreal half-life, allowing for a slow, sustained release of the anti-VEGF agent [64]. Rabbit models have demonstrated an estimated ocular half-life of approximately 10 to 12 days [65]. The Phase 3 DAYLIGHT (NCT04964089) and DAZZLE (NCT04049266) trials for nAMD demonstrated a favorable safety profile and no significant differences in BCVA and anatomical measures between monthly injections of KSI-301 5 mg, compared to bimonthly aflibercept 2 mg at week 48 [66,p.1], [67]. However, the Phase 3 GLEAM (NCT04611152) and GLIMMER (NCT04603937) studies failed to show noninferiority of KSI-301 compared to aflibercept for BCVA change in treatment-naïve DME patients. The GLOW study (NCT05066230) evaluating KSI-301 at a total of four doses in the first year and six month dosing in treatment-naïve, moderately severe to severe non-proliferative DR (NPDR) achieved its primary endpoint of greater than two-step improvement in DRSS compared to sham injection (41.1% vs 1.4%, $p < 0.01$) [68]. These results emphasize the potential durability advantage considering dosing was administered at baseline, week 8, week 20, and then six-month dosing intervals. Kodiak has initiated two additional Phase 3 studies: the GLOW2 study (NCT06270836) for DR, and the DAYBREAK study (NCT06556368) for nAMD. The GLOW2 expands on the work of the GLOW study with an additional third monthly loading dose at week 4 [69]. The DAYBREAK trial is a noninferiority study that aims to continue evaluating the efficacy, safety, and durability of KSI-301 and newly developed KSI-501 compared to bimonthly aflibercept [69]. Kodiak is also developing KSI-501, a biconjugate of a dual inhibitor trap antibody fusion (TAF) protein and a phosphorylcholine-based biopolymer. This product can inhibit both VEGF-A and IL-6, pivotal in abnormal angiogenesis and inflammation, respectively [70].

2.3. Hydrogel delivery systems

Hydrogels are multi-dimensional structures created through the chemical or physical crosslinking of polymer chains. These structures are quite versatile in that they can be constructed with natural biopolymers (alginate and chitosan) or synthetic polymers (PLA, PGA, and PLGA) and held together via physical (ionic bonds, hydrogen bonding, and van der Waals) and/or chemical (covalent bonds) crosslinking methods. This allows hydrogels to be designed to be compatible with many different environments and present with specific drug release/degradation patterns [71,72]. Thus, the application of hydrogels in ocular drug delivery is another promising solution for minimizing the treatment burden prevalent in many retinal diseases. To our knowledge, no FDA-approved intravitreal hydrogel products are yet available [73].

OTX-TKI (Axpaxli, Ocular Therapeutix, Bedford, MA, U.S.A.) is a bioresorbable intravitreal PEG hydrogel implant that includes axitinib, a small TKI that is a selective and potent inhibitor of VEGFR-1, VEGFR-2, and VEGFR-3. This hydrogel implant provides

a gradual release of axitinib over the span of six to 12 months [74]. The Phase I trials revealed that a single 600 μg OTX-TKI implant sustained similar visual acuity to bimonthly aflibercept at 12 months in patients with nAMD with an 89% reduction in the anti-VEGF injection rate. OTX-TKI was also well tolerated, with no reports of severe drug-related ocular or systemic adverse effects [75]. The Phase 3 SOL-1 (NCT06223958) trial is currently underway and is expected to be fully enrolled with all patients randomized by the end of 2024 [76]. This superiority study has a primary endpoint of proportion of subjects who maintain BCVA at week 36 compared to bimonthly aflibercept. The Phase 3 SOL-R study (NCT06495918) has begun enrollment to investigate repeat dosing of OTX-TKI every six months with the primary endpoint of non-inferiority in mean BCVA change from baseline compared to bimonthly aflibercept 2 mg [77].

2.4. Gene therapy

The retina has been pivotal in the development of gene-based therapy as far back as 1994 when researchers introduced a bacterial gene into mice retinal pigment epithelium (RPE) using an adenovirus vector and as recently as the FDA approval of voretigene neparvovec-rzyl (Luxturna, Spark Therapeutics, Philadelphia, PA, U.S.A.) for Leber congenital amaurosis (LCA) in 2017, the first FDA-approved gene therapy for inherited disease [78,79]. Since this monumental achievement, retinal gene therapy development has made significant advances, with researchers exploring the potential of using this delivery system beyond inherited retinal diseases. Theoretically, a therapeutic gene could be administered and integrated into a patient's cells to enhance the expression of a desired protein, such as endogenous anti-VEGF (Figure 2). This would allow for sustained production of anti-VEGF and alleviate the treatment burden of frequent intravitreal injections. Subretinal injection is the current standard for ocular gene therapy administration via pars plana vitrectomy (PPV). However, this procedure is associated with many potential complications, such as a macular hole and/or potential photoreceptor disruption associated with bleb creation, retinotomy with hemorrhage and/or fibrosis, retinal tear and detachment, and cataract. Thus, alternative pathways involving suprachoroidal and intravitreal administration are also being investigated to avoid such complications evident with PPV [81].

4D–150 (4D Molecular Therapeutics (4DMT), Emeryville, CA, U.S.A.) is a single-use, low-dose intravitreal gene therapy utilizing an evolved vector, R100, capable of infiltrating the internal limiting membrane to increase retinal transgene expression. The vector consists of a transgene cassette that expresses both aflibercept and a VEGF-C inhibitory RNAi to inhibit a total of four anti-angiogenic factors: VEGF-A, -B, -C, and placental growth factor (PlGF) [82]. Results from the Phase I PRISM trial (NCT05197270) revealed that all three dose cohorts of 3×10^{10}, 1×10^{10}, and 6×10^{9} vector genomes per eye (vg/eye) of 4D–150 had favorable safety profiles with no drug-related AEs or dose-limiting toxicities [83]. Furthermore, in the 3×10^{10} vg/eye high dose cohort, nAMD patients experienced a 96.7% overall reduction in mean annualized anti-VEGF injection rate at 36 weeks. The Phase 2 Prism trial (NCT05197270) expanded on these findings by demonstrating equivalent and stable BCVA outcomes and improved retinal anatomical variability with 4D–150 at a high dose compared to the bimonthly aflibercept arm. High dose 4D–150 was also associated with an 89% and 83% overall reduction in annualized anti-VEGF injection rate and a 63%

and 57% injection-free rate at 24 weeks and 52 weeks, respectively [84,85]. Following the positive initial results from PRISM trials, 4DMT was granted the Regenerative Medicine Advanced Therapy (RMAT) and Priority Medicines (PRIME) designations by the FDA and European Medicines Agency (EMA), respectively, with the aim of increasing collaboration on regulatory approval planning and expediting drug development [82]. 4DMT has already made plans and presented the design of the 4FRONT–1 Phase 3 clinical trial, a multicenter, randomized Phase 3 clinical trial comparing a single dose of 4D–150 3×10^{10} vg/eye to bimonthly aflibercept 2 mg in treatment-naïve nAMD patients. 4DMT anticipates initiation of the trial in the first quarter of 2025 [86].

2.5. Encapsulated cell therapy

Revakinagene taroretcel-lwey (Encelto, NT-501, Neurotech Pharmaceuticals, Cumberland, RI, U.S.A.) is a novel intravitreal implant utilizing an encapsulated cell therapy (ECT) platform to deliver ciliary neurotrophic factor (CNTF) that was recently approved in March 2025 for the treatment of Macular Telangiectasia Type 2 (MacTel) [87]. CNTF is a neuroprotective protein shown to promote the survival and maintenance of photoreceptors. The ECT platform contains a small, semi-permeable capsule with proprietary allogeneic retinal pigment epithelium cells that are genetically engineered to produce long-term, sustained delivery of therapeutic proteins, such as CNTF. The platform capsule is surgically inserted into the patient's vitreous and sutured to the sclera, allowing the CNTF to exit into the vitreous, while essential nutrients are able enter the capsule and the encapsulated RPE cells are protected from the host's immune system (Figure 3).

The approval of revakinagene taroretcel-lwey follows the positive results of the NTMT-03A (NCT03316300) and NTMT-03B (NCT03319849) Phase 3 trials investigating its efficacy and safety in participants with MacTel. The primary outcome of these trials was the rate of change in EZ loss area from baseline through month 24. Neurotech announced positive topline results with a 56.4% rate of reduction in Protocol A and a 29.2 % rate of reduction in Protocol B [89]. Pooled data from these studies revealed a 68% reduction in monocular reading speed loss over two years and a nearly 35% reduction in aggregate sensitivity loss with microperimetry data. Revakinagene taroretcel-lwey-treated eyes also demonstrated a one letter advantage in BCVA over two years [90]. The results of these trials and the approval of revakinagene taroretcel-lwey represent a significant breakthrough treatment for MacTel patients.

3. Suprachoroidal delivery

The suprachoroidal space (SCS) is a thin potential space situated between the sclera and choroid, encompassing the entire posterior segment of the eye from the ciliary body backward. For drug delivery, this space allows for a less invasive access point to the posterior region of the eye due to the posterior pole fluid flow, thereby bypassing some barriers with minimal off-target effects and enhancing safety (Figure 4). Furthermore, the relative insolubility and particle size of small-molecule suspensions can drive durability in the SCS [92,93]. Reliable access to SCS involves microneedles that have been designed to penetrate the sclera to facilitate the delivery of therapeutic agents into the

SCS without penetrating the vitreous. The intraocular pressure then drives the injectate circumferentially and posteriorly toward the lower pressure posterior suprachoroidal space to target chorioretinal tissues. Preclinical studies have supported high and durable levels of suprachoroidal-delivered medication to the chorioretina with limited anterior segment exposure [94–96]. In recent years, several clinical trials encompassing small-molecule suspensions to viral vector therapies have investigated the SCS as a viable target for drug delivery. Xipere (triamcinolone acetonide injectable suspension, Clearside Biomedical, Alpharetta, GA, U.S.A.), was the first FDA-approved suprachoroidal therapy for the treatment of macular edema associated with uveitis, paving the way for further potential small molecule suspension therapies.

The Phase 3 PEACHTREE trial (NCT02595398) of suprachoroidal triamcinolone acetonide for macular edema secondary to noninfectious uveitis demonstrated a significant improvement of at least 15 letters on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart in 47% of patients receiving suprachoroidal triamcinolone acetonide compared to only 16% in the sham group, highlighting the efficacy of the treatment. Furthermore, the injection procedure was well tolerated and there was no significant difference in the incidence of steroid-related complications between the treatment and control groups [97,98]. MAGNOLIA (NCT02952001) was a 48-week extension of the PEACHTREE trial and revealed that nearly 50% of patients who had received suprachoroidal triamcinolone acetonide did not require rescue treatment for nine months after the second injection. The mean BCVA gains were 12.1 letters with CST reductions of 174.5 μm at 48 weeks [99].

AU-011 (Aura Biosciences, Boston, MA, U.S.A.) is a papillomavirus-like drug conjugate therapy that selectively binds to heparin sulfate proteoglycans on the surface of choroidal melanoma cells and delivers belzupacap sarotalocan (bel-sar). This cytotoxic drug is then activated by infrared ophthalmic laser irradiation, leading to cell membrane damage and subsequent immune reactions, providing a long-term anti-melanotic cell immunogenicity [100]. Results from a Phase 2 clinical trial revealed that AU-011 achieved an 80% tumor control rate with favorable safety profiles [101]. Furthermore, despite the tumors being located near the macula and optic nerve, 90% of patients also maintained their BCVA. These results highlight the potential of this therapy, especially considering the current standard of care, radiotherapy, is associated with reductions in visual acuity of less than 20/200 in the treated eye of up to 87% of patients [101]. Aura is currently enrolling patients for the global, Phase 3, randomized CoMpass superiority trial (NCT06007690) to evaluate the suprachoroidal injection of high and low-dose bel-sar compared to sham control in nonmetastatic small and medium choroidal melanoma patients [102].

4. Subretinal delivery

The subretinal space is a region between the RPE layer and the photoreceptors, which has become of great interest to researchers in delivering gene- and cell-based therapies. Accessing this small area first requires conducting a vitrectomy to separate the posterior vitreous and then administering the drug subretinally via a retinotomy. This endeavor is highly invasive but allows for direct access to the RPE layer and the photoreceptors,

primarily affected by many retinal dystrophies [103]. Earlier preclinical research highlighted the potential of the subretinal space in delivering gene therapy via the preferred adeno-associated viruses (AAVs) [104,105], including the use of an AAV2 vector to carry a wild-type RPE65 gene that demonstrated the ability to effectively rehabilitate the retinal function in a canine model of LCA [106]. The success of this model would lead to the monumental Phase 3 clinical trials (NCT00999609) of voretigene neparvovec (AAV2 hRPE65v2, hereon VN).

The investigation of gene therapy delivery methods has also been expanded for treating various non-hereditary retinal diseases, utilizing a 'biofactory approach,' particularly AMD, DME, and DR [107]. ABBV-RGX-314 is a novel gene therapy intervention being developed by REGENXBIO (Rockville, MD, U.S.A.) and AbbVie (North Chicago, IL, U.S.A.) utilizing an AAV8 vector carrying a transgene encoding a ranibizumab-like anti-VEGF monoclonal antibody fragment. The therapy is administered via a single subretinal or suprachoroidal injection, allowing for cellular expression of anti-VEGF therapy within the retinal tissues. The Phase 1/2a, open-label, multiple-cohort, dose-escalation study found that subretinal delivery of RGX-314 was generally well-tolerated across all five dose levels in nAMD. Furthermore, BCVA and central retinal thickness (CRT) remained stable at six months [108]. Ongoing Phase 2b/3 trials, ATMOSPHERE (NCT04704921) and ASCENT (NCT05407636), are randomized, partially masked, controlled studies evaluating two dose levels of subretinal ABBV-RGX-314 against monthly intravitreal ranibizumab and bimonthly intravitreal aflibercept, respectively. The primary outcome of the trials is the mean change in BCVA from baseline to 54 weeks [109,110]. REGENXBIO has plans for the trials to support global regulatory submission in late 2025 and the first half of 2026 [111]. Simultaneously, REGENXBIO is evaluating the suprachoroidal delivery of ABBV-RGX-314 in the Phase 2 AAVIATE trial (NCT04514653) for nAMD patients [112].

5. Topical delivery

Topical drug administration is established as an effective delivery route for anterior segment eye diseases. Absorption of medications administered topically occurs through the corneal route or the transconjunctival/scleral route. Lipophilic medications are better absorbed through the cornea and conjunctiva relative to hydrophilic drugs. Furthermore, smaller molecules are better able to permeate through the cornea and sclera.

OCS-01 (Oculis, Zug, Switzerland) is a topical eyedrop utilizing Oculis' proprietry OPTIREACH® formulation of high concentration dexamethasone. The OPTIREACH® technology incorporates nanoparticle aggregates of γ-cyclodextrin to improve the solubility of lipophilic drugs in eyedrop formulations, increase their residence time on the eye surface, and help enable their passage to the posterior segment of the eye [113]. In a multicenter, randomized, Phase 2 study, topical OCS-01 achieved significantly greater decreases in central macular thickness than vehicle with greater visual improvement in eyes with lower baseline vision [114]. OCS-01 was overall well-tolerated; however, AEs were more common in the OCS-01 group (70.0% versus 53.3%), with intraocular pressure (IOP) increase occurring much more frequently (26.0% versus 0.0%). The DIAMOND (DIAbetic Macular edema patients ON a Drop) program is currently underway with the Phase 3 DIAMOND-1

(NCT05066997) and DIAMOND-2 (NCT06172257) trials to evaluate the efficacy and safety of topical OCS-01 in DME. Oculis recently announced the acceleration of patient enrollment in these trials, with approximately 70% of patients enrolled in DIAMOND-1 trial and approximately 40% of patients enrolled in DIAMOND-2 through early October [115]. The results of these pivotal trials will be highly anticipated as an effective topical therapy for DME would significantly reduce treatment burden due to improved patient comfort and safety, accessibility, and cost of treatment [116].

6. Systemic delivery

Systemic drug delivery to the retina and vitreous is limited by blood-ocular barriers, including the blood-aqueous and blood-retinal barriers [117]. The blood-retinal barrier is composed of the inner barrier of retinal capillary endothelial cells and the outer barrier of the retinal pigment epithelium layer, which limit and regulate access of mediation to the posterior segment. It has been estimated that due to these limitations, only approximately 1–2% of oral dose of a medication reaches the vitreous humor [117]. Intravenous administration of verteporfin (Visudyne, Bausch + Lomb, Vaughan, Ontario, Canada), a photosensitizing, pharmacological agent that is used for photodynamic therapy (PDT) is one of the few examples of systemic retinal therapies. Originally FDA approved in 2000 for treatment of subfoveal choroidal neovascularization secondary to nAMD, it was the standard of care for several years until anti-VEGF demonstrated superiority in the ANCHOR study (NCT00061594) [118,119]. Though PDT has mainly fallen out of favor in the treatment of nAMD, off-label use has been demonstrated in conditions such as central serous chorioretinopathy (CSC), various types of ocular hemangioma, and choroidal melanomas [120–122]. There are currently no ongoing Phase 3 clinical trials investigating oral or intravenous pharmacologic delivery in retinal disease.

6.1. Subcutaneous delivery

Advanced dry AMD can cause severe central vision loss in the form of foveal center-involving geographic atrophy (GA). Noncentral or extrafoveal GA can also cause significant visual impairment and presents the risk of progressing to involve the fovea. The emergence of intravitreal complement inhibitors has been a significant breakthrough in retina as the first treatment options available for advanced dry AMD with GA. These treatments now offer hope to slow the progression of a disease for patients who previously had no approved therapeutic options; however, currently approved complement inhibitors are limited by their requirement for chronic monthly or bimonthly intravitreal administration. This presents a tremendous treatment burden for patients and providers alike, similar to the need for frequent anti-VEGF intravitreal injections in retinal neovascular disease. Several therapies are under investigation that target the biochemical and pathophysiologic processes that play a role in the development of GA secondary to advanced AMD. Retinal mitochondrial dysfunction has been identified as a key player in the development and progression of AMD [123]. Risks factors such as cigarette smoke, lipofuscin accumulation, and complement dysregulation have all been implicated in retinal mitochondrial dysfunction that may increase risk for chronic retinal pathologies [124].

Elamipretide (Stealth BioTherapeutics, Needham, MA, U.S.A.) is a first-in-class mitochondria-targeted tetrapeptide that stabilizes the structure and function of the mitochondrial electron transport chain, thereby increasing cellular adenosine triphosphate (ATP) production and decreasing mitochondria-derived oxidants. Thus, the drug has been postulated as a potential modulator of the mitochondrial-mediated pathophysiologic processes involved in dry AMD [125]. Elamipretide is administered as a 40 mg (1 mL) subcutaneous injection in the abdominal area once daily. The injection is administered either by the patient or by a caregiver. The Phase 1 ReCLAIM (NCT02848313) study investigated the safety, tolerability, and feasibility of subcutaneouselamipretide in subjects with intermediate AMD, high-risk drusen, and noncentral GA [126,127]. The study found that subcutaneous administration of elamipretide was highly feasible with only mild to moderate AEs, most commonly injection site reactions. Furthermore, exploratory analyses demonstrate a positive effect on visual function, particularly under low-luminance (LL) conditions [126,127]. In the Phase 2 ReCLAIM-2 study (NCT03891875), daily subcutaneous elamipretide 40 mg failed to meet the primary endpoints of a mean change in LL BCVA and mean change in square root converted GA area, but did demonstrate a significant slowing of progressive ellipsoid zone (EZ) degradation or loss, a surrogate for photoreceptor damage [128]. The Phase 3 ReNEW (NCT06373731) and ReGAIN trials plan to evaluate the efficacy and safety of once-daily subcutaneous injections of elamipretide in participants with dry AMD [129,130]. The primary endpoint for the trials is the rate of change in the macular area of photoreceptor loss assessed by spectral domain-optical coherence tomography and EZ mapping. Stealth BioTherapeutics has begun enrolling and dosing in the ReNEW trial [129].

7. Conclusion

The field of ocular drug delivery continues to evolve rapidly, though significant challenges persist in developing optimal delivery systems for posterior segment diseases. The blood-retinal barrier remains a primary obstacle for systemic delivery, with only 1–2% of oral medications reaching the vitreous, while current standard intravitreal injections, despite their efficacy, carry risks of endophthalmitis and retinal detachment. This review, while focused primarily on late-stage clinical developments and recent approvals, highlights several promising approaches advancing through clinical development (Table 1). Sustained-release platforms, including both biodegradable and non-biodegradable implants, demonstrate potential for reducing treatment burden while maintaining therapeutic efficacy. Novel delivery routes such as suprachoroidal and subretinal administration offer targeted approaches particularly beneficial for gene therapy applications, while innovative topical delivery systems like the OPTIREACH® technology show promise for noninvasive posterior segment drug delivery, as evidenced by the Phase 2 results of OCS-01 and the ongoing DIAMOND program. It is important to note that comparative pharmacokinetic data across these diverse delivery systems remains limited. This gap in evidence creates challenges when attempting to directly compare the potential effectiveness of different approaches, particularly for newer modalities like subcutaneous delivery and gene therapy, where standardized pharmacokinetic parameters may not be readily applicable.

The field appears to be moving toward a more diversified approach where multiple delivery options may be available for specific conditions, allowing for personalized treatment strategies, though cost considerations and healthcare system integration pose ongoing challenges. Looking forward, sustained-release technologies are likely to become more prevalent, potentially reducing the burden of frequent intravitreal injections, while gene therapy delivery systems may provide 'one-and-done' treatments for some conditions, albeit with significant cost and accessibility considerations. Advancing these promising approaches will require continued collaboration between academic institutions, pharmaceutical companies, and clinicians, with priority research areas including the development of predictive models for treatment response, optimization of delivery systems for specific disease states, investigation of combination approaches, and improvement of cost-effectiveness. Multi-center collaborations and standardized outcome measures, including increased focus on patient-reported outcomes and quality of life measures, will be crucial for generating robust evidence to guide clinical implementation of new delivery systems and ensure that new technologies address both clinical efficacy and patient preferences.

8. Expert opinion

The current dominance of intravitreal injections in posterior segment drug delivery reflects a critical tension in ophthalmology between therapeutic efficacy and treatment burden. While direct intravitreal administration achieves optimal drug concentrations at the target tissue, the necessity for frequent injections poses significant challenges for both healthcare systems and patients. The field appears to be evolving along several promising trajectories, each with distinct advantages and limitations.

The development of sustained-release platforms represents perhaps the most immediate path to reducing treatment burden. Current Phase 3 trials of port delivery systems for ranibizumab exemplify this approach, potentially offering months of therapeutic effect from a single intervention. However, an operating room based procedure and the potential surgical complications associated with implantable devices, as well as the need for periodic refills suggest that this solution, while valuable, may not be suitable for all patients. The ideal sustained-release platform would combine the durability of current implants with a less invasive office-based delivery method – a goal that remains elusive but should drive future research.

Novel delivery routes show particular promise for specific applications. The OPTIREACH® technology's use of γ-cyclodextrin nanoparticles to enhance topical drug delivery represents a potentially transformative approach. The Phase 2 results for OCS-01, showing significant reduction in central macular thickness, suggest that effective topical delivery to the posterior segment may be achievable. The current DIAMOND program will be crucial in determining whether topical therapy can provide a viable alternative to intravitreal injections for conditions like DME.

Emerging subcutaneous delivery approaches, exemplified by elamipretide for dry AMD, represent an intriguing middle ground between local and systemic delivery. While the Phase

2 ReCLAIM-2 study did not meet its primary endpoints, the significant preservation of EZ integrity suggests that this route may offer unique advantages for certain therapeutic targets. The ongoing Phase 3 ReNEW and ReGAIN trials may help define the role of subcutaneous delivery in the treatment algorithm for dry AMD.

The development of targeted delivery methods like suprachoroidal and subretinal injection appears particularly promising for gene therapy applications. These approaches offer precise delivery to target tissues but face significant technical challenges and potential complications. The risk-benefit calculation for these more invasive approaches will likely restrict their use to conditions requiring single or very infrequent treatments, such as gene therapy interventions.

Looking ahead over the next 5–10 years, we anticipate several transformative developments in ocular drug delivery. The integration of drug delivery with real-time monitoring systems will likely emerge as a key advancement, enabling optimization of treatment timing and dosing. We expect to see the development of ‘smart’ delivery systems capable of responding to disease activity, alongside combination approaches that utilize multiple delivery routes to achieve optimal therapeutic effects. Novel formulations that can better penetrate ocular barriers while maintaining stability will also play a crucial role in advancing the field.

The most successful future therapies will likely combine innovations in both drug delivery and therapeutic agents. For example, the development of more stable molecules could reduce the frequency of administration needed, while improved delivery systems could maintain therapeutic levels more consistently. The current limitation of 1–2% bioavailability for systemic medications reaching the vitreous represents a particular challenge that, if overcome, could revolutionize treatment approaches. The advancement of the field will require focused research in several key areas. The development of predictive models for drug distribution and clearance in various delivery systems will be essential for optimizing new approaches. Standardization of outcome measures across delivery methods will enable better comparisons between different technologies, while investigation of patient-specific factors will help guide delivery system selection. Economic analyses will be crucial for guiding healthcare system implementation of novel delivery methods.

Success in these areas will require unprecedented collaboration between pharmaceutical companies, device manufacturers, and clinical researchers. The increasing burden of retinal diseases, driven by aging populations and the rising prevalence of diabetes, makes such collaboration not just desirable but essential. The ideal future state would offer clinicians a menu of delivery options that can be matched to individual patient needs, disease characteristics, and therapeutic goals. While this vision may be years from realization, current developments in topical, sustained-release, and targeted delivery systems suggest we are moving in the right direction. The key challenge will be balancing innovation with practical considerations of safety, cost, and implementation in real-world clinical settings.

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80. Toronto U of. English: figure 1. Schematic overview of how viruses (i.e. adenovirus) can be used to deliver recombinant genetic material to neurons, or other cell types within the nervous system. Steps include viral binding to cell membrane, endosomal packaging and breakdown,

delivery and integration of vector into host DNA, and ending with the expression of the desired protein. [Internet]. 2022 [cited 2024 Jan 31]. Available from: https://commons.wikimedia.org/wiki/File:Viral_mediated_delivery_of_genes_to_neurons_1.jpg

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Article highlights

- Conventional intravitreal injections effectively target posterior segment disease but impose significant treatment burden through frequent administration, creating challenges for patient adherence and healthcare systems.
- Novel intravitreal delivery therapies include reservoirs such as the ranibizumab port delivery system (Susvimo), polymer-based delivery (Duravyu, KSI-301, KSI-501), hydrogel delivery systems (Axpaxli), gene therapy (4D–150), and encapsulated cell therapy (Revakinagene taroretcel-lwey).
- Suprachoroidal delivery (Xipere, AU-011) and subretinal delivery (Luxturna, timrepigene emparvovec, cotoretigene toliparvovec, ABBV-RGX-314) offer drug delivery directly to the target chorioretinal tissue.
- Noninvasive techniques include subcutaneous (elamipretide) and topical delivery (OCS-01).

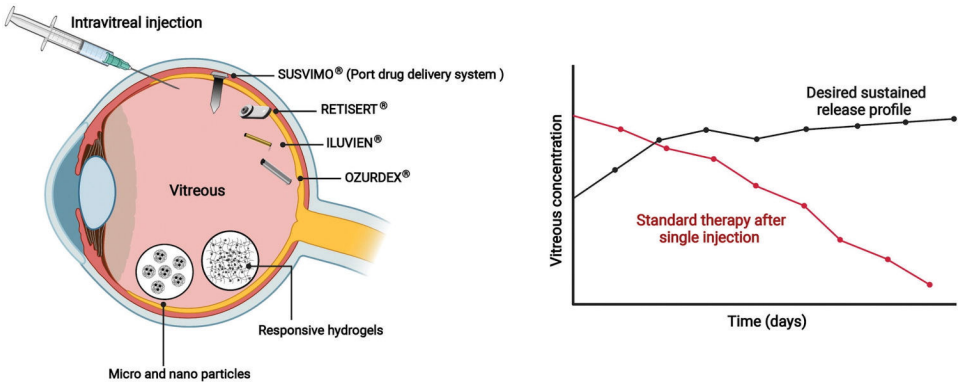

Figure 1.

Illustration of novel, investigative, sustained-release drug delivery technologies with hydrogel and micro/nanoparticles, and FDA-approved sustained-release therapies with Ozurdex® (dexamethasone implant, FDA approved in 2009), Retisert® (fluocinolone acetonide implant, FDA approved in 2005) Iluvien® (fluocinolone acetonide implant, FDA approved in 2014) and SUSVIMO® (ranibizumab port delivery system, FDA approved in 2021). The graph on the right exemplifies the preserved drug concentration within the vitreous compared to the relative rapid clearance of medication with standard intravitreal injection. From Alshaikh RA, Waeber C, Ryan KB. Adv Drug Deliv Rev. 2022;187:114342 [6]. Licensed for reuse under the creative commons CC-BY license.

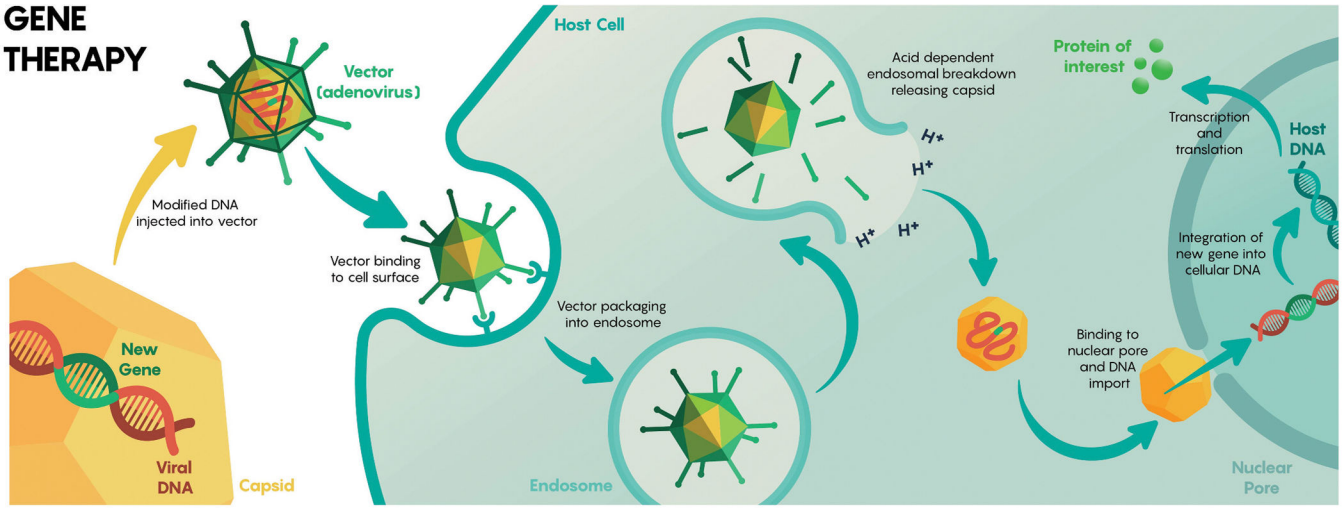

Figure 2.

Overview of adenovirus-mediated delivery of recombinant genetic material to host cells for endogenous expression of a desired protein. From: https://commons.wikimedia.org/wiki/File:Viral_mediated_delivery_of_genes_to_neurons_1.jpg [80]. Licensed for reuse under the creative commons attribution-share alike 4.0 international license.

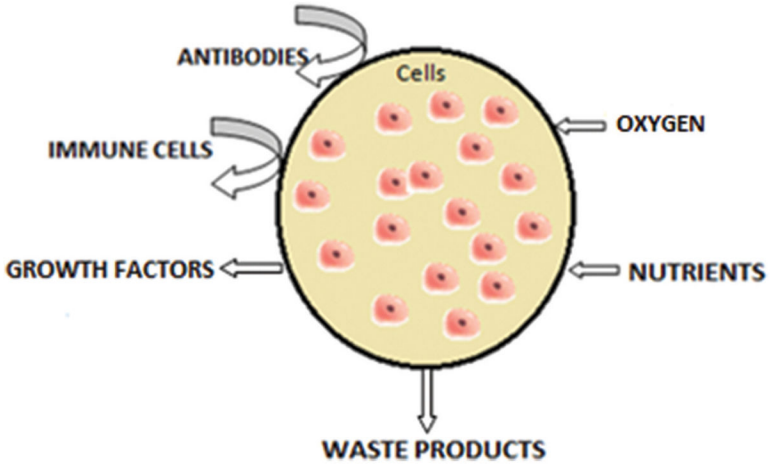

Figure 3.
Schematic illustrating encapsulated cell therapy. From: https://commons.wikimedia.org/wiki/File:Cell_capsule_schematic.png [88]. Licensed for reuse under the creative commons attribution-share alike 4.0 international license.

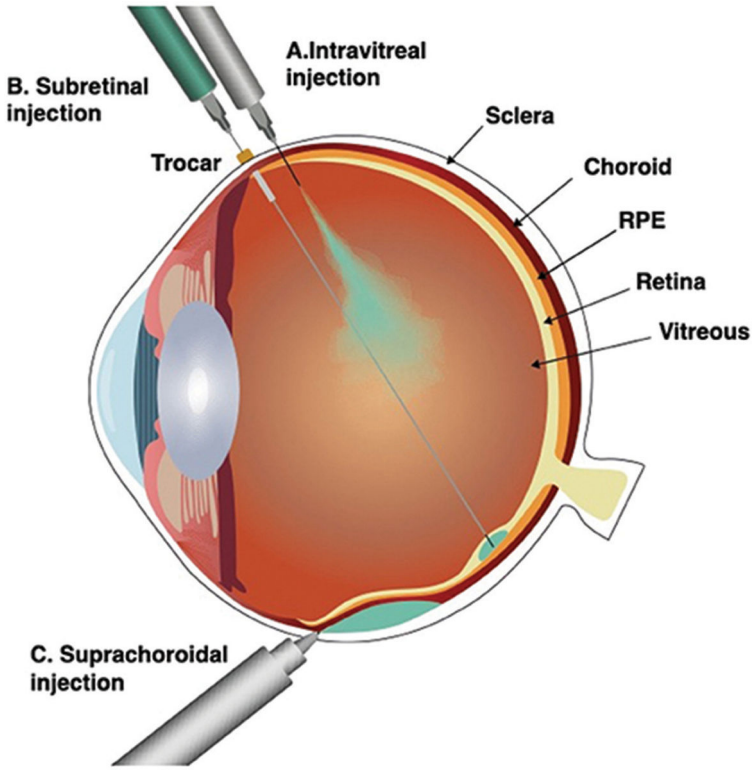

Figure 4.

Illustration comparing (A) intravitreal injection, (B) subretinal injection, and (C) suprachoroidal injection through a microneedle. From Ladha R, Caspers LE, willermain F, de smet MD. Front med [internet]. 2022 Mar 23 [cited 2024 Nov 30];9 [91]. Licensed for reuse under the creative commons CC-BY license.

Table 1.

Clinical characteristics of novel drug delivery therapies for retinal disease in phase 3 development or FDA approved within the past five years.

Drug	Company	Indication	Mechanism of action	Duration of action	Phase of development
Intravitreal delivery					
Port delivery system, ranibizumab (Susvimo)	Genentech (San Francisco, CA, U.S.A.)	nAMD, DME, DR	VEGF-A inhibition	Up to 24 weeks	FDA approved
EYP-1901 (Duravyu): vorolanib implant, bio-erodible Durasert E platform	EyePoint Pharmaceuticals (Watertown, MA, U.S.A.)	nAMD	TKI: inhibition of all isoforms of VEGFR and PDGFR	Six months or longer	Phase 3
KSI-301 (tarcocimab tedromer)	Kodiak Sciences (Palo Alto, CA, U.S.A.)	nAMD, DME, RVO	VEGF-A, VEGF-B, PIGF inhibition	Up to six months	Phase 3
KSI-501	Kodiak Sciences (Palo Alto, CA, U.S.A.)	nAMD, DME	IL-6, VEGF-A, VEGF-B, PIGF inhibition	Up to six months	Phase 3
OTX-TKI (Axpaxli): axitinib implant, PEG hydrogel delivery system	Ocular Therapeutix (Bedford, MA, U.S.A.)	nAMD	TKI: VEGFR-1, VEGFR-2, VEGFR-3 inhibition	Six months or longer	Phase 3
4D-150	4D Molecular Therapeutics (Emeryville, CA, U.S.A.)	nAMD	VEGF-A, VEGF-C, PlGF inhibition	Indefinite	Phase 3
Revakinagene taroretcel-lwey (Encelto, NT-501): encapsulated cell therapy platform	Neurotech Pharmaceuticals (Cumberland, RI, U.S.A.)	MacTel	CNTF delivery	Two years or longer	Phase 3
Suprachoroidal delivery					
Xipere: triamcinolone acetonide injectable suspension	Clearside Biomedical (Alpharetta, GA, U.S.A.)	Macular edema associated with uveitis	Corticosteroid hormone receptor agonist	Nine months	FDA approved
AU-011: belzupacap sarotalocan targeted delivery	Aura Biosciences (Boston, MA, U.S.A.)	Choroidal melanoma	Selectively binds to choroidal melanoma cells, activated by infrared ophthalmic laser irradiation	Three initial cycles	Phase 3
Subretinal delivery					
ABBV-RGX-314	REGENXBIO (Rockville, MD, U.S.A.), AbbVie (North Chicago, IL, U.S.A.)	nAMD	VEGF-A inhibition	Indefinite	Phase 3
Subcutaneous delivery					
Elamipretide	Stealth BioTherapeutics (Needham, MA, U.S.A.)	Dry AMD	Mitochondria-targeted tetrapeptide	Daily	Phase 3
Topical delivery					
OCS-01: high concentration dexamethasone	Oculis (Zug, Switzerland)	DME	Corticosteroid hormone receptor agonist	Daily	Phase 3

Ab breviations: AMD, age-related macular degeneration; CNTF, ciliary neurotrophic factor; DME, diabetic macular edema; DR, diabetic retinopathy; FDA, Food and Drug Association; IL-6, interleukin 6; MacTel, macular telangiectasia; nAMD, neovascular age-related macular degeneration; PDGFR, platelet-derived growth factor receptor; PlGF, placental growth factor; RVO, retinal vein occlusion; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.