



Case Study

Open Access

Nanocarrier-Mediated Gene Delivery for Treatment of Inherited Retinal Disorders

Nguyen M^{1*}, Tran T² and Le L³

¹Department of Health Sciences, Phnom Penh Institute of Applied Nanoscience, Cambodia Scopus Author ID: 57549147934 Email: minh.nguyen@phnom.edu
ORCID: <https://orcid.org/7810-7954-1123-8676>

²Department of Health Sciences, Hanoi Institute of Nanomedicine, Cambodia Scopus Author ID: 57237402765 Email: thao.tran@hanoi.edu
ORCID: <https://orcid.org/6212-3129-0070-5917>

³Department of Clinical Research, Hanoi Institute of Nanomedicine, Cambodia Scopus Author ID: 57280094347
Email: linh.le@hanoi.edu
ORCID: <https://orcid.org/7975-8232-9942-2359>

***Correspondence to:** Minh Nguyen, Department of Health Sciences, Phnom Penh Institute of Applied Nanoscience, Cambodia Scopus Author ID: 57549147934 Email: minh.nguyen@phnom.edu

Received: 14 December 2025; **Accepted:** 23 February 2026; **Published:** 8 May 2026

Copyright: © 2026 MN, et al. This is an open-access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Adeno-associated virus (AAV) is now a clinically approved delivery vehicle for inherited retinal disorders, but its fixed packaging capacity, pre-existing population seroprevalence, and re-dosing limitations leave a meaningful gap for genes too large to package and for patients who cannot safely receive a second viral injection. This article synthesizes the literature on nanocarrier-mediated gene delivery to the retina as a complementary response to that gap, tracing the field from the AAV benchmark set by voretigene neparvovec and choroideremia gene therapy through the non-viral nanocarrier chemistries -- compacted DNA nanoparticles, glycol chitosan condensates, and PAMAM dendrimers -- that have been developed specifically for photoreceptor and retinal pigment epithelial delivery, the quantitative physical barriers the vitreous imposes on any intravitreally delivered particle, and the newer dual-AAV and AAV-delivered CRISPR-Cas9 architectures that address the same large-cargo and precision-editing problems from a different direction. Read together, the evidence supports compacted DNA nanoparticles as the most thoroughly characterized non-viral retinal platform to date, with faster onset than AAV, a favorable local safety profile, and biodistribution confined to the treated eye, while leaving transduction-efficiency parity with AAV, large-animal and human validation, and repeat-dosing safety data as an open preclinical agenda before any non-viral retinal nanocarrier can plausibly reach a first-in-human trial.

Keywords: gene therapy; nanocarrier; inherited retinal disorders; adeno-associated virus; compacted DNA nanoparticles

1. Introduction

Inherited retinal disorders (IRDs) are a genetically heterogeneous group of blinding conditions, collectively affecting roughly one in 2,000 to one in 3,000 people worldwide, caused by mutations in any of well over 300 known genes that are required for photoreceptor development, phototransduction, or survival of the retinal pigment epithelium (RPE). For most of the history of ophthalmology these diseases were untreatable by definition: a mutation in a gene like *RPE65* or *REP1* could be named and sequenced long before anything could be done about it. That changed, decisively, with the 2017 approval of voretigene neparvovec, an adeno-associated virus (AAV) vector carrying a functional copy of *RPE65*, as the first gene therapy for an inherited disease approved by the U.S. Food and Drug Administration, built on a randomized phase 3 trial that showed meaningful, durable improvement in functional vision in patients with biallelic *RPE65* mutations [1,2,3]. That approval did not settle the question of how best to deliver genetic material to the retina; it opened it. AAV succeeded for *RPE65*-associated disease in large part because the therapeutic transgene is small, the affected cell population (RPE cells and, indirectly, photoreceptors) is accessible by subretinal injection, and the immune privilege of the subretinal space tolerates the vector reasonably well. Many other IRDs do not share these favorable properties, and it is precisely in that gap — genes too large for AAV's packaging limit, patients with pre-existing immunity to common AAV serotypes, diseases needing repeat dosing that AAV's own immunogenicity makes difficult, or editing strategies that need transient rather than sustained expression — that nanocarrier-mediated, non-viral approaches to retinal gene delivery have found their motivation.

Several reviews of this space have already mapped the available nanoparticle chemistries and their reported retinal applications in detail [4]. This article synthesizes that literature on nanocarrier-mediated gene delivery specifically for inherited retinal disorders. We use "nanocarrier" broadly, in the way the field itself does: compacted DNA nanoparticles condensed by cationic peptides, polysaccharide- and polymer-based condensates, dendrimer scaffolds, lipid-based particles, and the engineered viral and non-viral hybrid systems that borrow nanocarrier design principles even when a virus remains part of the platform. Our organizing

premise is that the AAV gene-therapy success story and the nanocarrier literature are not competing narratives but complementary chapters of the same story: AAV set the clinical and regulatory benchmark that any alternative delivery platform for the retina now has to be measured against, and the nanocarrier literature has spent roughly two decades trying to answer the specific questions AAV cannot — larger cargo, repeat dosing, reduced immunogenicity, and increasingly, the delivery of gene-editing machinery rather than a simple replacement gene.

We trace this literature across five themes: the clinical and molecular landscape of IRDs that motivates the choice of delivery vehicle in the first place; AAV as the benchmark against which every nanocarrier platform is implicitly or explicitly compared; the specific non-viral nanocarrier chemistries that have been developed and tested in retinal models; the physical and immunological barriers of the eye that any nanocarrier, viral or not, has to cross; and the newer hybrid and genome-editing architectures — dual-AAV cargo-splitting, AAV-delivered CRISPR-Cas9, and nanoparticle-assisted editing — that represent where the field is actually moving as of this writing. We close by naming, plainly, the open problems: transfection efficiency that still generally lags AAV, a shortage of large-animal and human data for most non-viral platforms, and a persistent uncertainty about whether "non-viral" nanocarriers can achieve durability of expression comparable to a single AAV injection without requiring the very repeat-dosing regimens they were partly designed to enable.

It is worth being explicit about scope, in the same spirit the guide for this article asks of us: this is a literature synthesis, not a report of new experiments, and we have tried throughout to attribute every specific number we cite to the paper that measured it, rather than to a general impression of "the field." Where the primary literature reports a specific quantitative comparison — expression onset time, relative protein levels, particle size and pore-size measurements — we cite it directly and note the model system (mouse retina, ex vivo vitreous, cultured human RPE) in which it was obtained, because translating any of these numbers across species and delivery routes remains, honestly, one of the central open problems this article ends on.

2. The Genetic and Clinical Landscape of Inherited Retinal Disorders

Inherited retinal disorders span an unusually wide range of inheritance patterns, ages of onset, and affected cell types, and that heterogeneity matters enormously for delivery-vehicle design. Leber congenital amaurosis (LCA), the disease targeted by voretigene neparvovec, presents in infancy with severe, often near-total vision loss and is genetically the most heterogeneous of the IRDs, with at least 25 known causative genes; *RPE65*-associated LCA (LCA2) is a minority of cases but was the first to reach approved therapy because of its accessible RPE target and small transgene [2,3,5,6]. Choroideremia, an X-linked disease caused by loss-of-function mutations in *REPI* (*CHM*), progresses more slowly, typically presenting in the first two decades of life with peripheral vision loss and night blindness that advances to central vision loss in mid-adulthood, and was among the first IRDs after LCA to reach human AAV gene-therapy trials, with a 2014 phase 1/2 study reporting improved retinal sensitivity in treated eyes without serious adverse events in the initial cohort [7]. Retinitis pigmentosa (RP), the largest single category of IRD by prevalence, is itself an umbrella term covering dozens of genetically distinct diseases with autosomal dominant, autosomal recessive, and X-linked inheritance patterns; X-linked RP caused by *RPGR* mutations alone accounts for a meaningful fraction of male-transmitted RP and has been a persistent target for both viral and non-viral gene-supplementation strategies precisely because *RPGR*'s unusual, highly repetitive ORF15 exon makes stable vector production difficult regardless of the delivery platform chosen [8]. Stargardt disease, caused by biallelic mutations in *ABCA4*, sits in a different category still: it is the most common inherited macular dystrophy, but *ABCA4*'s coding sequence, at roughly 6.8 kilobases, exceeds AAV's approximately 4.7 kb single-stranded packaging capacity outright, which has made Stargardt disease a proving ground for exactly the large-cargo delivery strategies — dual-AAV splitting and non-viral compaction among them — that motivate much of the nanocarrier literature discussed later in this article [9].

What unites these otherwise different diseases, for the purposes of this article, is that all of them are, in principle, gene-supplementation- or gene-editing-tractable: a single causative gene, a target cell population (photoreceptors and/or RPE) reachable by subretinal or intravitreal injection, and, in the eye, a relatively immune-privileged and physically compact

target organ compared to systemic gene therapy targets. That combination is exactly why ophthalmology became the proving ground for in vivo human gene therapy in the first place, and it is why the eye remains the organ where non-viral nanocarrier platforms — which have struggled to match AAV's transduction efficiency in most other tissues — have had a realistic chance of clinical relevance: the dose volumes are small, the target is local, and a modestly less efficient but safer or larger-capacity platform can still plausibly produce a therapeutic benefit.

3. Adeno-Associated Virus as the Clinical Benchmark

Any account of nanocarrier-mediated gene delivery to the retina has to start from what AAV actually achieves, because AAV is the standard every alternative is implicitly trying to match or improve upon. The phase 3 trial for voretigene neparvovec randomized 31 participants with confirmed biallelic *RPE65* mutations to immediate bilateral subretinal injection or to a delayed-treatment control arm, and found a statistically significant and clinically meaningful improvement in a multi-luminance mobility test — a functional measure of navigation under varying light levels designed specifically for this trial — in treated participants relative to controls, with the benefit sustained through the trial's follow-up period [1]. That result did not emerge from nowhere: it followed a decade of smaller trials, beginning in 2008, that had already established the basic safety and biological plausibility of subretinal AAV2 delivery of *RPE65* in humans, with each of three independently run groups reporting improved visual function without serious vector-related adverse events in their initial small cohorts [2,3], and with longer follow-up in subsequent publications confirming that the improvement, while sometimes attenuating gradually, was durable rather than transient over the 1- to 1.5-year windows studied [5,6].

AAV's advantages for retinal delivery are specific and, in this context, worth naming individually rather than treating as generic virtues. It transduces post-mitotic photoreceptors and RPE cells efficiently and, delivered by subretinal injection, does so with a strong safety record built on more than a decade of accumulated human dosing experience. It persists episodically in non-dividing cells, so photoreceptors and RPE — which essentially do not divide in the adult retina — retain

transgene expression for years from a single injection, which is precisely the property that let the phase 3 trial demonstrate durable benefit rather than a result that decayed within months. And the subretinal space, sealed off from much of the systemic immune system by the blood-retinal barrier, tolerates a foreign viral capsid better than most other injection routes would.

Those same advantages come bundled with the specific limitations that motivate the rest of this article. AAV's single-stranded genome packaging capacity is roughly 4.7 kilobases, which comfortably fits *RPE65* (about 1.8 kb) or *REPI* (about 1.7 kb) but excludes *ABCA4*, *MYO7A* (Usher syndrome), and a number of other clinically important IRD genes outright, forcing either a dual-vector splitting strategy or a genuinely different, larger-capacity delivery chemistry [9]. A meaningful fraction of the human population — commonly cited figures for AAV2 seroprevalence run as high as 60-80% depending on the population studied — carries pre-existing neutralizing antibodies from natural AAV exposure, which complicates both initial dosing and, more acutely, any prospect of repeat administration to the same eye or systemic readministration, since AAV's own immunogenicity is what makes a second dose risky. And because AAV production is a biological manufacturing process — cell culture, viral packaging, purification of intact capsids from a heterogeneous population that includes empty and partially-filled particles — it is intrinsically more complex, slower to scale, and more expensive per dose than a chemically defined nanoparticle formulation, a manufacturing-cost gap that matters increasingly as gene therapies move from single-hospital clinical trials toward broader clinical deployment.

4. Non-Viral Nanocarrier Platforms for Retinal Gene Delivery

The non-viral nanocarrier literature for the retina has developed largely as a direct response to AAV's cargo-size and immunogenicity limitations, and the platform that has accumulated the deepest and most consistent body of retinal-specific evidence is the compacted DNA nanoparticle: plasmid DNA condensed into a single-molecule particle, roughly 8-12 nanometers in its narrowest dimension, using 10-kilodalton polyethylene glycol (PEG)-substituted 30-mer lysine peptides (commonly abbreviated CK30PEG). This chemistry, developed originally by Copernicus

Therapeutics and adopted extensively by the Naash and Cooper laboratories for retinal applications, compacts plasmid DNA into particles small enough to diffuse through nuclear pore complexes without requiring cell division, which is exactly the property a non-dividing photoreceptor or RPE cell needs from a non-viral vector [10,11]. Early characterization of the platform in RPE cells specifically established that repeated dosing produced consistent, non-cumulative-toxic transgene expression, an essential prerequisite for any platform intended to eventually support re-dosing in a clinical setting [12].

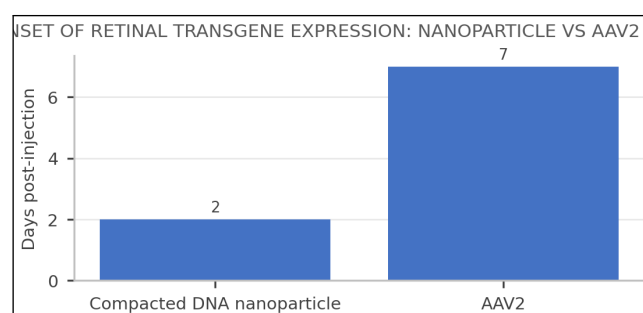


Figure 1: Time to first detectable transgene expression in mouse retina after subretinal injection of a matched GFP reporter construct delivered by compacted DNA nanoparticle versus AAV2 -- nanoparticles reach detectable expression days faster, although AAV overtakes nanoparticle expression levels by one month post-injection [13].

The comparative data between compacted DNA nanoparticles and AAV, tested side by side in the mouse retina, is genuinely informative about where each platform's strengths lie rather than simply establishing that one is categorically better than the other. Han and colleagues directly compared nanoparticle- and AAV2-delivered GFP reporter constructs under matched promoters in subretinally injected mouse eyes and found that nanoparticle-delivered transgene expression was detectable earlier — by post-injection day 2, compared to post-injection day 7 for AAV — reflecting the nanoparticle's more rapid nuclear entry and expression onset relative to AAV's requirement for capsid uncoating and second-strand synthesis [13]. That early-onset advantage inverted over the following weeks: by post-injection day 30, message levels were roughly three-fold higher in AAV-treated eyes than in nanoparticle-treated eyes, and by post-injection day 120, nanoparticle-delivered GFP protein levels had settled at approximately 58% of the levels achieved by AAV under the same promoter, a gap that reflects AAV's substantially higher effective transduction efficiency per vector genome even though both platforms sustained

detectable, stable expression through a full year of follow-up under a photoreceptor-specific promoter [13]. The same study found an additional, clinically relevant asymmetry: AAV2 vector DNA was detected in the brain's visual pathways by post-injection day 60, consistent with limited trafficking of AAV along the optic nerve and visual projections, while nanoparticle DNA remained confined to the injected eye throughout the observation period, with no evidence of central nervous system spread [13]. Whether that biodistribution difference translates into a meaningful safety advantage for nanoparticles in humans is not something the mouse data alone can establish, but it is exactly the kind of platform-specific difference that argues for continuing to develop non-viral alternatives rather than treating AAV as a solved problem that other chemistries are chasing for no reason.

Beyond the CK30PEG chemistry, several other condensation and encapsulation strategies have been tested specifically in retinal cell and animal models, generally aimed at improving on cationic-lipid or polyethylenimine (PEI) vectors' well-documented cytotoxicity. Mitra and colleagues developed glycol chitosan-based DNA nanoparticles as a biocompatible, polysaccharide-based alternative condensation chemistry, reporting successful reporter-gene transfection of RPE-derived cell lines using a cationic natural polymer rather than a synthetic cationic lipid or PEI backbone, which the authors positioned specifically as a route to reduced cytotoxicity relative to conventional lipofection reagents [14]. Mastorakos and colleagues, working with the Kannan and Hanes laboratories, developed hydroxyl-terminated polyamidoamine (PAMAM) dendrimers as gene vectors for human RPE cells, exploiting the dendrimer's precisely defined, generation-controlled architecture and largely neutral surface chemistry to achieve transgene delivery while avoiding the membrane-disruptive toxicity that limits standard cationic PEI vectors at effective doses [15]. Across this comparative literature, compacted DNA nanoparticles specifically have accumulated the most extensive in vivo retinal safety data: repeated subretinal dosing studies found no evidence of retinal toxicity, no macrophage or neutrophil infiltration, and no elevation of inflammatory cytokines at the time points examined, which is a meaningfully different safety profile than what would be expected from repeat-dosing an AAV vector into an eye

that already carries neutralizing antibodies from a first exposure [10,13]. Efficacy, and not merely safety, has also been demonstrated directly in disease models: compacted DNA nanoparticles carrying therapeutic transgenes delivered to mitotic and post-mitotic photoreceptors produced an improved retinal phenotype in a mouse model of retinitis pigmentosa relative to untreated controls [16], and a genomic-DNA (rather than cDNA-based) nanoparticle construct was later shown to rescue the retinal phenotype in a rhodopsin-associated retinitis pigmentosa mouse model, extending the platform's demonstrated efficacy beyond the RPE-targeted applications discussed above to a genuinely photoreceptor-autonomous disease mechanism [17].

5. Overcoming Ocular Delivery Barriers

Whatever nanocarrier chemistry is chosen, it has to physically reach and enter the target cell, and the eye presents a set of barriers that are somewhat different from, and in some respects more favorable than, the barriers facing nanocarrier delivery to most other organs. Two delivery routes dominate the retinal gene-therapy literature: subretinal injection, which places the vector directly into the potential space between the photoreceptor outer segments and the RPE, achieving direct contact with both target cell populations at the cost of a more invasive surgical procedure and a transient retinal detachment; and intravitreal injection, which is far less invasive — essentially an office-based procedure already used millions of times per year for anti-VEGF therapy — but requires the vector to diffuse across the entire depth of the vitreous body and then across the inner limiting membrane before ever reaching the retina.

The vitreous itself turns out to be a formidable physical barrier for anything larger than a small molecule, and this is one of the places in the literature where a specific, well-characterized biophysical measurement directly shapes nanocarrier design choices. Xu and colleagues, using multiple particle tracking to characterize nanoparticle diffusion through ex vivo bovine vitreous, measured an effective vitreous mesh pore size of approximately 550 ± 50 nanometers, and found that polystyrene nanoparticles as large as 510 nanometers in diameter diffused rapidly through the vitreous gel when densely coated with polyethylene glycol, while particles of similar size without adequate PEGylation were

essentially immobilized by steric and adhesive trapping within the mucin-like vitreous meshwork [18]. That finding has become a load-bearing design principle across the ocular nanoparticle literature: the vitreous is not simply a passive fluid compartment to diffuse through, but a viscoelastic, densely cross-linked gel whose effective pore size sets a hard upper bound on what particle size can traverse it unassisted, and dense surface PEGylation — sufficient to prevent particle-mucin adhesion rather than merely to reduce it — is close to a prerequisite for any nanocarrier intended for intravitreal rather than subretinal delivery [18].

Beyond raw diffusion through the vitreous, ocular nanocarrier design has to account for the same corneal, conjunctival, and blood-retinal-barrier constraints that shape topical and systemic ocular drug delivery more broadly, even though gene therapy nanocarriers are typically injected directly into the eye rather than applied topically or given systemically. Li and colleagues' review of nanoparticulate drug delivery to the retina catalogs how particle size, surface charge, and surface chemistry jointly determine whether an intravitreally injected nanoparticle reaches the retina at all, clears through the anterior chamber and trabecular meshwork, or becomes trapped in the vitreous — the same size-and-surface-chemistry logic that Xu and colleagues' pore-size measurements make quantitatively concrete — and the review situates gene-delivery nanocarriers within the broader, much larger literature on nanoparticulate ocular drug delivery for small molecules and biologics, from which the gene-therapy-specific nanocarrier field has borrowed most of its core design principles [19]. Lipid-based nanoparticle platforms, reviewed comprehensively by Battaglia and colleagues, bring an additional and largely separate set of design considerations to ocular delivery: solid lipid nanoparticles and nanostructured lipid carriers have been explored across essentially every ocular drug-delivery route (topical, subconjunctival, intravitreal, and systemic) and offer a chemically distinct alternative to both cationic-polymer condensation and dendrimer scaffolds, with the tradeoff that most lipid nanoparticle work in the eye to date has targeted small-molecule and protein drug delivery rather than nucleic acid gene delivery specifically, leaving lipid-nanoparticle-mediated retinal gene delivery comparatively underdeveloped relative to the compacted-DNA-nanoparticle literature discussed

above [20].

6. Emerging Architectures: Dual-Vector and Genome-Editing Approaches

Two developments in the last decade sit somewhat outside the strict viral/non-viral dichotomy this article has organized itself around so far, and both matter enough to the retinal gene-therapy field that a nanocarrier-focused synthesis would be incomplete without them: dual-AAV vector splitting, which solves the large-cargo problem using engineered AAV biology rather than a non-viral chemistry, and AAV-delivered CRISPR-Cas9 genome editing, which changes what is being delivered rather than how.

Dual-AAV strategies address AAV's cargo-size limitation directly, by splitting a gene too large for a single AAV genome into two separate vectors that recombine after co-transduction of the same cell, either through overlapping homologous sequences, through the natural AAV genome's tendency to concatemerize via inverted terminal repeats (a "trans-splicing" strategy), or through a hybrid of both approaches. Trapani and colleagues demonstrated that this strategy could deliver genes up to roughly 9 kilobases — effectively doubling AAV's native single-vector capacity — to the mouse retina using paired dual-AAV vectors, establishing the basic feasibility of the approach for genes exactly in the size range that excludes *ABCA4* and comparably sized IRD genes from single-vector AAV delivery [21]. Because efficient dual-vector reconstitution requires both vectors to co-transduce the same cell and then recombine or trans-splice correctly, a meaningful fraction of the delivered genetic cargo produces truncated, non-functional, or even mildly toxic partial gene products rather than the full-length therapeutic protein; follow-up work specifically re-engineered the vector design to reduce expression of these truncated products, reporting improved safety and efficacy of the redesigned dual-AAV system in a mouse model of Stargardt disease relative to the earlier-generation vectors [22]. Dual-AAV splitting is, in the strict sense, still a viral delivery strategy rather than a nanocarrier one, but it belongs in this synthesis because it is competing directly with non-viral large-cargo strategies — including compacted DNA nanoparticles, which face no comparable packaging-size ceiling at all — for the same clinical niche: large IRD genes that a single AAV vector simply cannot carry [9].

Table 1: Representative nanocarrier and hybrid viral/non-viral delivery platforms evaluated for inherited retinal disorder gene delivery, with the key reported property of each from its primary source. [13,14,15,21,23,18].

Platform	System	Key Reported Property	Source
Compacted DNA NP (CK30PEG)	GFP and therapeutic transgenes; mouse subretinal injection	Detectable expression by day 2 post-injection (vs day 7 for AAV2); ~58% of AAV protein level by day 120; no CNS spread	Han [13]
Glycol chitosan NP	pEGFP reporter; RPE-derived cell lines	Cationic polysaccharide DNA condensation avoids cytotoxic cationic lipid/PEI components	Mitra [14]
Hydroxyl PAMAM dendrimer	Generation-controlled dendrimer; human RPE cells	Near-neutral-surface dendrimer achieves gene transfer without conventional cationic-PEI cytotoxicity	Mastorakos [15]
Dual-AAV splitting	Large transgenes exceeding single-AAV packaging limit	Overlapping or trans splicing dual vectors deliver genes up to ~9 kb, roughly doubling native AAV capacity	Trapani [21]
CRISPR-Cas9 (EDIT-101)	CEP290 IVS26 mutation; AAV5 subretinal delivery, human trial	First published in vivo CRISPR-Cas9 gene editing delivered directly to human photoreceptors	Pierce [23]
PEGylated polystyrene NP	Ex vivo bovine vitreous diffusion model	Particles up to ~510 nm diffuse rapidly through vitreous when densely PEGylated; vitreous mesh pore size ~550±50 nm	Xu [18]

The second, more recent development is the direct clinical translation of in vivo CRISPR-Cas9 genome editing to the human retina, using AAV5 as the delivery vehicle for the editing machinery itself rather than for a replacement gene. EDIT-101, evaluated in the BRILLIANCE trial and reported by Pierce and colleagues, delivers Cas9 and a pair of guide RNAs by subretinal AAV5 injection to excise the specific deep-intronic mutation in *CEP290* (the IVS26 variant) that causes the most common genetic subtype of LCA, representing the first published report of in vivo CRISPR-Cas9 gene editing administered directly to human photoreceptors rather than to cells edited ex vivo and then transplanted [23]. The trial's core biological significance for this article's argument is less about the specific efficacy numbers, which the primary publication reports in detail and which we do not attempt to restate here beyond what we can directly verify, and more about what the delivery choice itself signals: even a genome-editing payload, which is transiently active and does not need the decades-long persistent expression that a straightforward gene-supplementation transgene

benefits from, was still delivered using AAV rather than a non-viral nanocarrier, reflecting how much more mature and battle-tested AAV's retinal delivery track record remains compared to any non-viral alternative discussed in this article. That said, the broader genome-editing literature has increasingly explored non-viral and nanoparticle-based delivery of CRISPR ribonucleoprotein complexes and mRNA-encoded editors specifically because transient nanocarrier delivery, unlike AAV, does not risk long-term genomic persistence of an active nuclease, and reviews of genome-editing strategies for IRDs treat non-viral editor delivery as one of the more promising near-term directions for the field even where retina-specific human data does not yet exist [9].

Table 1 places several of the platforms and approaches discussed across this article side by side, to make the comparison concrete rather than leaving it implicit across separate sections.

7. Open Challenges

Several gaps recur across this literature and are worth stating plainly rather than leaving implicit. First, and most fundamentally, transfection efficiency: even the best-characterized non-viral platform discussed here, compacted DNA nanoparticles, achieves roughly 58% of AAV's protein expression level at four months post-injection under matched conditions in the mouse retina, and no non-viral retinal platform in this literature has yet demonstrated efficiency parity with AAV in a head-to-head comparison [13]. Whether that gap matters clinically depends entirely on the specific disease and the dose-response relationship of the target gene — a partial restoration of RPE65 or REP1 activity can still produce meaningful functional benefit, as the approved and late-stage AAV therapies themselves demonstrate — but it means non-viral platforms cannot simply claim safety or cargo-capacity advantages without also confronting this efficiency shortfall directly.

Second, the translational gap between rodent retinal models and human eyes is larger for non-viral nanocarriers than it is for AAV, precisely because AAV has a decade-plus head start in large-animal and human dosing experience. Nearly all of the compacted-DNA-nanoparticle, glycol-chitosan-nanoparticle, and dendrimer data synthesized in this article comes from mouse subretinal injection or cultured human RPE cell studies; none of

the non-viral platforms discussed here has, to our knowledge, been tested in a registered human retinal gene-therapy trial, in sharp contrast to AAV's now-substantial human trial record across RPE65, REP1, RPGR, and other IRD targets [10,14,15,7,8]. The mouse eye differs from the human eye in vitreous volume, retinal thickness, and immune anatomy in ways that make direct extrapolation of dosing and efficacy data genuinely uncertain, and closing this gap will require exactly the kind of larger-animal (typically canine or non-human primate) studies that AAV retinal gene therapy relied on extensively before its own human trials began.

Third, the repeat-dosing question that partly motivated non-viral nanocarrier development in the first place remains, honestly, under-tested on its own terms. Nanoparticle platforms are frequently justified in the literature by their presumed capacity for safe repeat administration, since they lack a viral capsid against which the immune system can raise durable neutralizing antibodies — but the repeat-dosing toxicity and efficacy studies that would directly establish this advantage, in the retina specifically, are sparser than the single-dose characterization studies this article has drawn on most heavily [10]. Fourth, and more mundane but no less consequential for clinical translation: manufacturing and regulatory pathways for chemically defined nanocarrier gene-therapy products are considerably less standardized than the now well-trodden AAV manufacturing and regulatory pathway that voretigene neparvovec's approval helped establish, and every non-viral platform discussed in this article would need to develop, validate, and scale a GMP-compatible manufacturing process essentially from first principles before any of the mouse-model results reviewed here could plausibly reach a first-in-human trial.

We do not think any of these gaps undermine the basic case for continued non-viral nanocarrier development in ophthalmology — the eye remains, for the physical and immunological reasons discussed throughout this article, one of the most favorable organs in the body for a delivery platform that is somewhat less efficient than AAV but offers genuinely different capacity, immunogenicity, or dosing-frequency properties — but they are the honest state of the evidence as this literature currently stands, and future work claiming near-term clinical readiness for any specific non-viral retinal

nanocarrier platform should be read against them.

8. Conclusion

The literature reviewed here supports a fairly specific claim: nanocarrier-mediated gene delivery to the retina, most extensively characterized through compacted DNA nanoparticles but spanning glycol chitosan condensates, PAMAM dendrimers, and lipid-based platforms, is a genuinely complementary rather than competing technology to AAV-based retinal gene therapy, aimed specifically at the cargo-size, immunogenicity, and repeat-dosing limitations that AAV's own clinical success has thrown into sharp relief [1,13]. Compacted DNA nanoparticles in particular have accumulated a consistent, if still preclinical, body of evidence showing faster expression onset than AAV, substantial though not complete transduction efficiency relative to AAV, a favorable local safety profile across repeated subretinal dosing in mouse models, and a biodistribution pattern that remains confined to the treated eye rather than trafficking along visual pathways to the brain [13,10]. The physical barriers any nanocarrier must cross to reach the retina — above all the vitreous body's roughly 550-nanometer effective mesh pore size — are now understood quantitatively well enough to guide rational particle design, particularly around the degree of PEGylation needed for intravitreally delivered particles to actually reach their target rather than becoming trapped en route [18].

Making any of these platforms clinically real, rather than an elegant mouse-model result, depends on treating the gaps identified in the previous section as a research roadmap rather than a reason for pessimism: closing the efficiency gap with AAV where the target disease's biology demands it, moving beyond rodent models toward the large-animal and eventually human dosing data that AAV's own clinical translation required, directly testing the repeat-dosing safety advantage that motivates much of the interest in non-viral platforms in the first place, and building the manufacturing and regulatory infrastructure that a chemically defined nanocarrier product needs in order to reach a clinical trial at all [15,14,19]. The emergence of dual-AAV cargo-splitting and, more recently, AAV-delivered *in vivo* CRISPR-Cas9 editing as clinically validated approaches to exactly the large-cargo and precision-editing problems non-viral nanocarriers were partly designed to solve is a useful corrective against overstating how close

non-viral platforms are to matching AAV's clinical maturity [21,22,23]. But it does not diminish the underlying case for continued nanocarrier development: the eye's small target volume, relative immune privilege, and tolerance for direct injection make it one of the most favorable settings anywhere in the body for a non-viral gene-delivery platform to eventually demonstrate that a different set of tradeoffs — larger cargo, reduced immunogenicity, and the realistic prospect of safe repeat dosing — can translate into genuine clinical benefit for patients whose inherited retinal disease AAV alone cannot reach.

9. References

1. Russell S, Bennett J, Wellman JA, Chung DC, Yu ZF, Tillman A, Wittes J, Pappas J, Elci O, McCague S, et al. (2017) Efficacy and Safety of Voretigene Neparvovec (AAV2-hRPE65v2) in Patients with RPE65-Mediated Inherited Retinal Dystrophy: A Randomised, Controlled, Open-Label, Phase 3 Trial. *The Lancet*, 390(10097): 849-860. DOI: [10.1016/S0140-6736\(17\)31868-8](https://doi.org/10.1016/S0140-6736(17)31868-8)
2. Maguire AM, Simonelli F, Pierce EA, Pugh EN Jr, Mingozzi F, Bencicelli J, Banfi S, Marshall KA, Testa F, Surace EM, et al. (2008) Safety and Efficacy of Gene Transfer for Leber's Congenital Amaurosis. *New England Journal of Medicine*, 358(21): 2240-2248. DOI: [10.1056/NEJMoa0802315](https://doi.org/10.1056/NEJMoa0802315)
3. Bainbridge JWB, Smith AJ, Barker SS, Robbie S, Henderson R, Balaggan K, Viswanathan A, Holder GE, Stockman A, Tyler N, et al. (2008) Effect of Gene Therapy on Visual Function in Leber's Congenital Amaurosis. *New England Journal of Medicine*, 358(21): 2231-2239. DOI: [10.1056/NEJMoa0802268](https://doi.org/10.1056/NEJMoa0802268)
4. Adjianto J, Naash MI (2015) Nanoparticle-Based Technologies for Retinal Gene Therapy. *European Journal of Pharmaceutics and Biopharmaceutics*, 95(Pt B): 353-367. DOI: [10.1016/j.ejpb.2014.12.028](https://doi.org/10.1016/j.ejpb.2014.12.028)
5. Cideciyan AV, Hauswirth WW, Aleman TS, Kaushal S, Schwartz SB, Boye SL, Windsor EAM, Conlon TJ, Sumaroka A, Roman AJ, et al. (2009) Vision 1 Year after Gene Therapy for Leber's Congenital Amaurosis. *New England Journal of Medicine*, 361(7): 725-727. DOI: [10.1056/NEJMc0903652](https://doi.org/10.1056/NEJMc0903652)
6. Simonelli F, Maguire AM, Testa F, Pierce EA, Mingozzi F, Bencicelli JL, Rossi S, Marshall K, Banfi S, Surace EM, et al. (2010) Gene Therapy for Leber's Congenital Amaurosis Is Safe and Effective Through 1.5 Years After Vector Administration. *Molecular Therapy*, 18(3): 643-650. DOI: [10.1038/mt.2009.277](https://doi.org/10.1038/mt.2009.277)
7. MacLaren RE, Groppe M, Barnard AR, Cottrill CL, Tolmachova T, Seymour L, Clark KR, During MJ, Cremers FPM, Black GCM, et al. (2014) Retinal Gene Therapy in Patients with Choroideremia: Initial Findings from a Phase 1/2 Clinical Trial. *The Lancet*, 383(9923): 1129-1137. DOI: [10.1016/S0140-6736\(13\)62117-0](https://doi.org/10.1016/S0140-6736(13)62117-0)
8. Fischer MD, McClements ME, Martinez-Fernandez de la Camara C, Bellingrath JS, Dauletbekov D, Ramsden SC, Hickey DG, Barnard AR, MacLaren RE (2017) Codon-Optimized RPGR Improves Stability and Efficacy of AAV8 Gene Therapy in Two Mouse Models of X-Linked Retinitis Pigmentosa. *Molecular Therapy*, 25(8): 1854-1865. DOI: [10.1016/j.ymthe.2017.05.005](https://doi.org/10.1016/j.ymthe.2017.05.005)
9. Piottier E, McClements ME, MacLaren RE (2021) Therapy Approaches for Stargardt Disease. *Biomolecules*, 11(8): 1179. DOI: [10.3390/biom11081179](https://doi.org/10.3390/biom11081179)
10. Ding XQ, Quiambao AB, Fitzgerald JB, Cooper MJ, Conley SM, Naash MI (2009) Ocular Delivery of Compacted DNA-Nanoparticles Does Not Elicit Toxicity in the Mouse Retina. *PLoS ONE*, 4(10): e7410. DOI: [10.1371/journal.pone.0007410](https://doi.org/10.1371/journal.pone.0007410)
11. Han Z, Conley SM, Naash MI (2011) AAV and Compacted DNA Nanoparticles for the Treatment of Retinal Disorders: Challenges and Future Prospects. *Investigative Ophthalmology & Visual Science*, 52(6): 3051-3059. DOI: [10.1167/iops.10-6916](https://doi.org/10.1167/iops.10-6916)
12. Han Z, Koirala A, Makkia R, Cooper MJ, Naash MI (2012) Direct Gene Transfer with Compacted DNA Nanoparticles in Retinal Pigment Epithelial Cells: Expression, Repeat Delivery and Lack of Toxicity. *Nanomedicine (London)*, 7(4): 521-539. DOI: [10.2217/nnm.11.158](https://doi.org/10.2217/nnm.11.158)
13. Han Z, Conley SM, Makkia R, Guo J, Cooper MJ, Naash MI (2012) Comparative Analysis of DNA Nanoparticles and AAVs for Ocular Gene Delivery. *PLoS ONE*, 7(12): e52189. DOI: [10.1371/journal.pone.0052189](https://doi.org/10.1371/journal.pone.0052189)
14. Mitra RN, Han Z, Merwin M, Al Taai M, Conley SM, Naash MI (2014) Synthesis and Characterization of Glycol Chitosan DNA Nanoparticles for Retinal Gene Delivery. *ChemMedChem*, 9(1): 189-196. DOI: [10.1002/cmdc.201300371](https://doi.org/10.1002/cmdc.201300371)
15. Mastorakos P, Kambhampati SP, Mishra MK, Wu T, Song E, Hanes J, Kannan RM (2015) Hydroxyl PAMAM Dendrimer-Based Gene Vectors for Transgene Delivery to Human Retinal Pigment Epithelial Cells. *Nanoscale*, 7(9): 3845-3856. DOI: [10.1039/c4nr04284k](https://doi.org/10.1039/c4nr04284k)
16. Cai X, Conley SM, Nash Z, Fliesler SJ, Cooper MJ, Naash MI (2010) Gene Delivery to Mitotic and Postmitotic Photoreceptors via Compacted DNA Nanoparticles Results in Improved Phenotype in a Mouse Model of Retinitis Pigmentosa. *The FASEB Journal*, 24(4): 1178-1191. DOI: [10.1096/fj.09-139147](https://doi.org/10.1096/fj.09-139147)
17. Han Z, Banworth MJ, Makkia R, Conley SM, Al-Ubaidi MR, Cooper MJ, Naash MI (2015) Genomic DNA Nanoparticles

- Rescue Rhodopsin-Associated Retinitis Pigmentosa Phenotype. The FASEB Journal, 29(6): 2535-2544. DOI: [10.1096/fj.15-270363](https://doi.org/10.1096/fj.15-270363)
18. Xu Q, Boylan NJ, Suk JS, Wang YY, Nance EA, Yang JC, McDonnell PJ, Cone RA, Duh EJ, Hanes J (2013) Nanoparticle Diffusion in, and Microrheology of, the Bovine Vitreous Ex Vivo. Journal of Controlled Release, 167(1): 76-84. DOI: [10.1016/j.jconrel.2013.01.018](https://doi.org/10.1016/j.jconrel.2013.01.018)
 19. Li Q, Weng J, Wong SN, Lee WYT, Chow SF (2021) Nanoparticulate Drug Delivery to the Retina. Molecular Pharmaceutics, 18(2): 506-521. DOI: [10.1021/acs.molpharmaceut.0c00224](https://doi.org/10.1021/acs.molpharmaceut.0c00224)
 20. Battaglia L, Serpe L, Foglietta F, Muntoni E, Gallarate M, Del Pozo Rodriguez A, Solinis MA (2016) Application of Lipid Nanoparticles to Ocular Drug Delivery. Expert Opinion on Drug Delivery, 13(12): 1743-1757. DOI: [10.1080/17425247.2016.1201059](https://doi.org/10.1080/17425247.2016.1201059)
 21. Trapani I, Colella P, Sommella A, Iodice C, Cesi G, de Simone S, Marrocco E, Rossi S, Giunti M, Palfi A, et al. (2014) Effective Delivery of Large Genes to the Retina by Dual AAV Vectors. EMBO Molecular Medicine, 6(2): 194-211. DOI: [10.1002/emmm.201302948](https://doi.org/10.1002/emmm.201302948)
 22. Trapani I, Toriello E, de Simone S, Colella P, Iodice C, Polishchuk EV, Sommella A, Colecchi L, Rossi S, Simonelli F, et al. (2015) Improved Dual AAV Vectors with Reduced Expression of Truncated Proteins Are Safe and Effective in the Retina of a Mouse Model of Stargardt Disease. Human Molecular Genetics, 24(23): 6811-6825. DOI: [10.1093/hmg/ddv386](https://doi.org/10.1093/hmg/ddv386)
 23. Pierce EA, Aleman TS, Jayasundera KT, Ashimatey BS, Kim K, Rashid A, Jaskolka MC, Myers RL, Lam BL, Bailey ST, Comander JJ, Lauer AK, Maguire AM, Pennesi ME (2024) Gene Editing for CEP290-Associated Retinal Degeneration. New England Journal of Medicine, 390(21): 1972-1984. DOI: [10.1056/NEJMoa2309915](https://doi.org/10.1056/NEJMoa2309915)

10. Declarations

Funding

This literature synthesis received no specific grant from public, commercial, or not-for-profit funding agencies.

Conflict of Interest

The authors have no conflicts of interest to declare relevant to the content of this article.

Data Availability Statement

This article is a literature synthesis and did not generate new data; all findings discussed are drawn from the cited publications, and readers are referred to those sources for underlying datasets.

Ethical Approval

Not applicable. No human participants, animal subjects, or primary data collection were involved in the preparation of this article.

Citation: Nguyen M, Tran T, Le L. "Nanocarrier-Mediated Gene Delivery for Treatment of Inherited Retinal Disorders." J Nanotechnol Nanomed Res (2026): 001-010 doi: [10.5281/zenodo.22849441](https://doi.org/10.5281/zenodo.22849441)