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Review Article

From bench to bedside: translational advances, therapeutic targets, and delivery strategies in diabetic retinopathy

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Abstract: Diabetic retinopathy (DR) is a leading cause of preventable blindness in adults of working age. Anti-vascular endothelial growth factor (anti-VEGF) therapy is the reference standard for diabetic macular edema (DME), yet in randomized cohorts, approximately 30-40% of DME eyes still show central macular thickening after six months of continuous treatment. In proliferative DR (PDR), the corresponding limitation is recurrence after treatment interruption rather than primary non-response, and these two patterns should not be conflated. This review examines translational research in DR across four domains. First, we review mechanistic work on the neurovascular unit, metabolic memory and its epigenetic substrate, the gut-retina axis, and human platforms including induced pluripotent stem cell (iPSC)-derived retinal organoids and clustered regularly interspaced short palindromic repeats (CRISPR) editing. Second, we discuss therapeutic targets beyond VEGF, including the nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome and related inflammatory pathways, neuroprotection, complement activation, the angiopoietin-2 (Ang2)/Tie2 axis, and non-coding RNA (ncRNA) networks. Third, in preclinical pharmacology, we regard delivery as the rate-limiting step and analyze in detail why lipid nanoparticle and N-acetylgalactosamine (GalNAc) conjugation strategies, which transformed hepatic RNA interference, have not translated to the retina, and what the terminated bevasiranib, PF-04523655, and iCo-007 programmes imply for trial design. Fourth, clinical translation, including cytokine biomarkers, artificial intelligence (AI)-based screening, combination regimens, and sustained-release implants. Evidence derived from age-related macular degeneration (AMD), including complement inhibition, stem cell transplantation, and photovoltaic implants, is evaluated separately, and its transferability to DR is assessed in light of differences in affected compartment, pathogenic driver, patient age, and expected treatment duration. We conclude that the principal obstacles in DR are no longer mechanistic but concern cell-type-specific delivery, early-phase trial design, and endpoint standardization, and we specify the evidence each candidate class should generate before clinical development proceeds.

Keywords: Diabetic retinopathy, translational medicine, drug delivery, non-coding RNA, neuroprotection

Introduction

Diabetic retinopathy (DR) is a microvascular complication of diabetes mellitus (DM) and remains one of the most common causes of irreversible visual impairment in adults of working age. A pooled analysis of 59 population-based studies estimated that 22.27% of people with diabetes have some degree of DR, corresponding to about 103 million affected individuals in 2020, and projected that this number will approach 161 million by 2045 as the diabetic population expands and survival improves [1]. Vision-threatening forms, namely proliferative diabetic retinopathy (PDR) and diabetic macular edema (DME), account for a disproportionate share of diabetes-related visual disability [2]. Because the retina is affected long before patients notice symptoms, and because screening coverage is uneven even in high-income settings, a large fraction of disease is still detected at a stage where treatment can only limit further loss rather than restore function [3, 4].

The current therapeutic armamentarium for DR rests on three pillars: panretinal or focal laser photocoagulation, intravitreal corticosteroids,

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and inhibition of vascular endothelial growth factor (VEGF). Each of these has a well-documented evidence base, yet each also has recognized ceilings. Laser destroys retinal tissue to preserve central vision. Corticosteroids raise intraocular pressure and accelerate cataracts. Anti-VEGF therapy - now the reference standard - involving DME and an accepted alternative to laser in PDR, requires repeated intravitreal injections, and a consistent subset of eyes showing residual edema or persistent neovascular activity despite treatment [5, 6]. None of the three modalities addresses the neurodegenerative, inflammatory, and metabolic processes that precede and accompany the vascular lesions.

Translational medicine provides a useful frame for thinking about why this gap persists. As originally articulated, translational research describes the bidirectional movement of knowledge between laboratory discovery, clinical investigation, and population health, together with the infrastructure that makes such movement possible [7, 8]. Subsequent work has refined the concept into a staged model, from mechanistic discovery through first-in-human studies, efficacy trials, implementation, and finally population-level impact [9, 10]. What the staged model makes visible is that failure can occur at any transition, and the reasons for failure at one stage are rarely the same as those at another.

In DR, the mechanistic literature has expanded far faster than the therapeutic literature. Retinal neurodegeneration, glial reactivity, complement activation, mitochondrial dysfunction, epigenetic memory, and non-coding RNA (ncRNA) networks have all been mapped in considerable detail, largely in rodent models and in cultured human cells [11]. Very few of these findings have produced an approved intervention. The bottlenecks are partly biological, since rodent retinas do not develop proliferative disease, and partly pharmaceutical, since the posterior segment is difficult to reach and the eye tolerates only small volumes and low doses. A third bottleneck is methodological: outcome measures used in mechanistic studies, such as acellular capillary counts or vascular permeability indices, do not map cleanly onto the visual-function endpoints that regulators accept.

A further reason to adopt a translational rather than a purely mechanistic frame is that the existing DR review literature is unevenly distributed. Reviews of pathogenesis and clinical management are numerous and frequently updated. Reviews that examine the interface between the two, asking why particular mechanisms have or have not yielded treatments and what specifically failed when they did not, are scarce. The consequence is that individual negative results, such as the discontinuation of an ocular nucleic acid program or a negative neuroprotection trial, are recorded in the primary literature but rarely analyzed collectively; consequently, the same design errors recur. We have therefore given deliberate weight to failed and terminated programs alongside successful ones, on the view that in a field where most therapeutic candidates do not reach patients, the informative signal lies as much in the pattern of failures as in the small number of successes.

This review examines where DR research currently stands along that translational path. We organize the material into four parts. The first covers in vitro and in vivo mechanistic work, with attention to the model systems now available (**Figure 1**). The second surveys therapeutic targets beyond VEGF and grades the evidence behind each. The third addresses preclinical pharmacology, with an emphasis on delivery, which we regard as the rate-limiting step for most of the newer modalities. The fourth covers clinical translation, including diagnostics, combination regimens, and device-based approaches. Throughout, we distinguish evidence generated in DR from evidence extrapolated from other retinal diseases, particularly age-related macular degeneration (AMD), and we state explicitly where such extrapolation is and is not defensible. **Figure 2** outlines the translational strategies considered across these four parts, from mechanistic discovery through delivery engineering to clinical implementation. We identified literature through PubMed and Web of Science searches using terms for DR combined with terms for translational research, drug delivery, ncRNA, neuroprotection, complement, and artificial intelligence. Priority was given to primary reports and English-language clinical trials; older work was retained where it remains the definitive source.

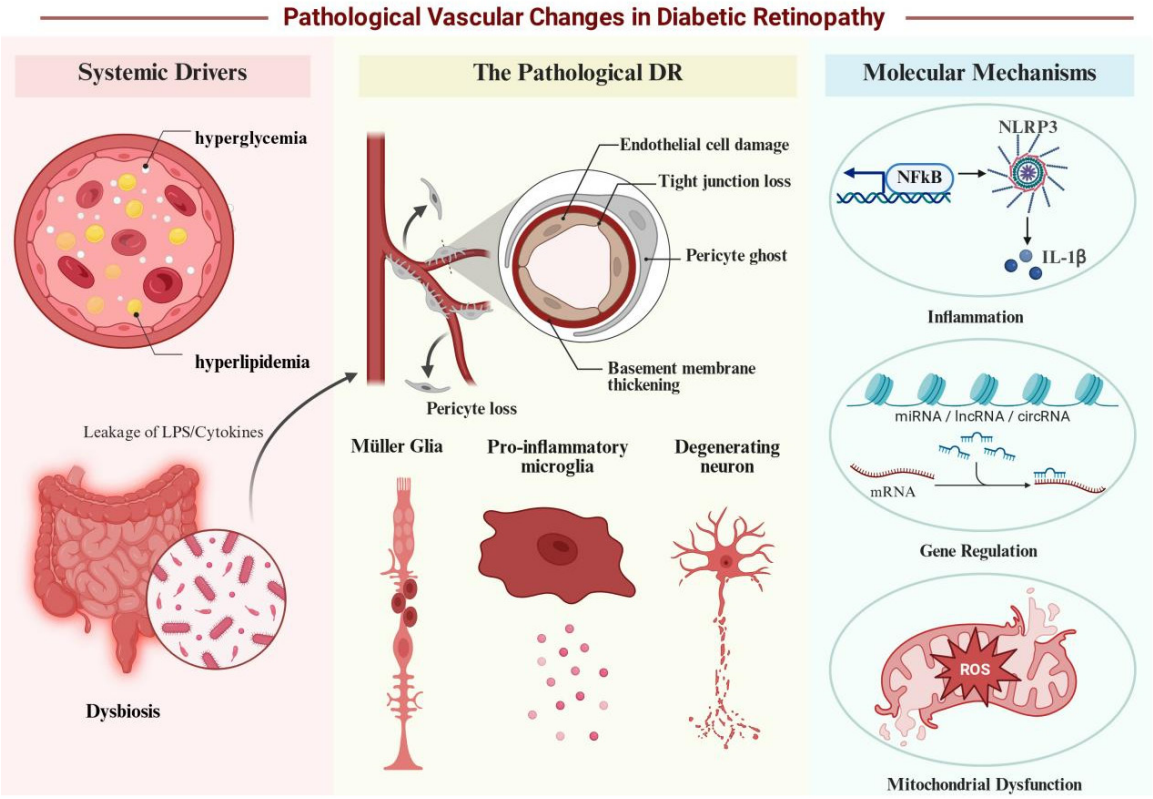


Figure 1. Advances in the pathogenesis of diabetic retinopathy. From systemic drivers, the pathological DR, and molecular mechanisms three perspectives, the basic mechanisms of DR can be clearly understood.

In vivo and in vitro studies

The neurovascular unit and glial cells

The conceptual shift from viewing DR as a pure microangiopathy to viewing it as a disease of the retinal neurovascular unit (NVU) is now well established. The NVU comprises neurons, macroglia, microglia, pericytes, and endothelial cells that jointly regulate blood flow and maintain the inner blood-retinal barrier [12]. Histopathological series had long documented pericyte dropout and acellular capillaries as the defining lesions of early DR [13], but functional and structural evidence of neuronal injury preceding these changes has accumulated steadily. Apoptosis of retinal ganglion cells (RGCs) and thinning of the inner retinal layers can be detected in diabetic rodents within weeks of hyperglycemia onset and in human donor eyes without clinically apparent retinopathy [14]. Whether neurodegeneration causes the vascular lesions or merely accompanies them remains contested, and the answer probably differs between type 1 and type 2 disease [15].

Glial cells sit at the center of this debate. Müller cells span the full retinal thickness and normally buffer extracellular potassium, recycle glutamate, and supply lactate to photoreceptors. Under sustained hyperglycemia they become reactive, upregulate glial fibrillary acidic protein, lose glutamine synthetase activity, and secrete VEGF and inflammatory mediators directly into the perivascular space [16]. Their regenerative potential is also constrained: recent work showed that intercellular transfer of the homeobox protein Prox1 from neighboring neurons actively suppresses the latent regenerative program of mammalian Müller glia, and that blocking this transfer restores some proliferative competence [17]. Microglia follow a parallel trajectory, migrating from the inner plexiform layer toward the outer retina and adopting an amoeboid, cytokine-secreting phenotype. Pharmacological suppression of this phenotype with minocycline reduces caspase-3 activation and proinflammatory cytokine expression in diabetic rodents [18], and natural compounds such as crocin produce similar effects through PI3K/Akt signaling [19]. These experi-

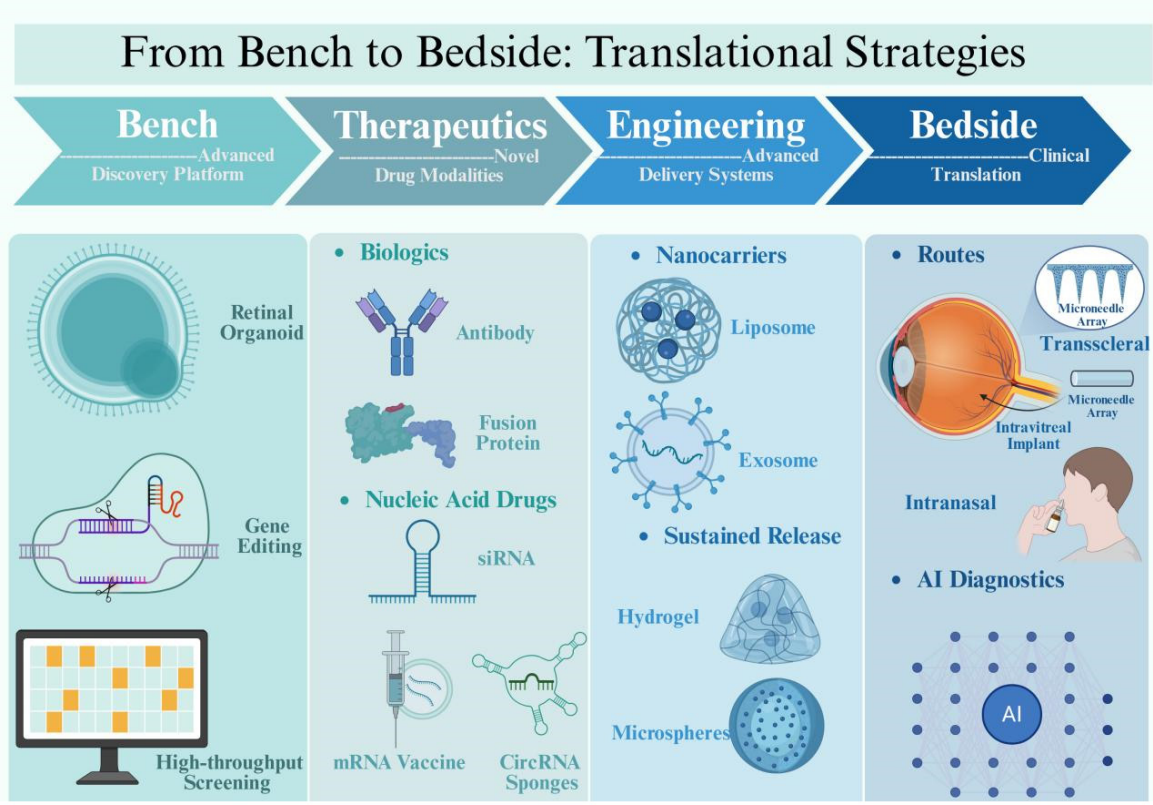


Figure 2. Detailed strategies for translational medicine. Translational medicine offers limitless opportunities in converting laboratory insights into clinical applications.

ments establish that glial activation is modifiable; they do not establish that modifying it in humans will preserve vision, and no glia-directed agent has yet reached a registrational DR trial.

Metabolic dysregulation and epigenetic regulation

More than two decades ago, the biochemical consequences of hyperglycemia in retinal cells were integrated into a unifying scheme in which mitochondrial superoxide overproduction activates four downstream pathways: increased polyol flux, formation of advanced glycation end-products (AGEs), activation of protein kinase C (PKC) isoforms, and increased hexosamine flux [20]. Each arm has been individually validated in retinal endothelial cells, pericytes, and Müller glia. Dyslipidemia contributes independently, with oxidized low-density lipoprotein and ceramide species amplifying endothelial injury and disrupting tight-junction assembly [21]. Pharmacological attempts to translate this scheme have been largely disappointing: aldose reductase inhibitors and the PKC-β inhibitor ruboxistaurin produced encouraging preclinical data but equivocal clinical results, and none entered routine practice.

Part of the explanation lies in metabolic memory, the persistence of diabetic complications after glycemic control is restored. Epigenetic mechanisms provide the most credible substrate for this phenomenon. Hyperglycemia induces stable changes in DNA methylation at mitochondrial and antioxidant gene loci, alters histone methylation and acetylation at the promoters of inflammatory genes, and reshapes ncRNA expression, and several of these marks persist for months after normoglycemia is reestablished [22]. Oxidative stress and epigenetic modification appear to reinforce one another, with mitochondrial DNA damage and impaired mitochondrial biogenesis both driving and responding to chromatin change [23]. The practical implication is that the therapeutic window for metabolic intervention may close earlier than glycemic targets alone would suggest, which argues for treating the epigenetic layer

as a target in its own right rather than as a downstream readout.

Metabolic memory is not a laboratory abstraction. In the Diabetes Control and Complications Trial (DCCT) and its observational extension, the Epidemiology of Diabetes Interventions and Complications (EDIC) study, patients originally assigned to intensive glycemic control continued to show lower rates of retinopathy progression for decades, even after the two treatment arms had converged to similar glycated hemoglobin levels [24]. A comparable legacy effect has been described in type 2 diabetes. Two implications follow. Clinically, the period of early glycemic exposure carries disproportionate weight, which strengthens the case for aggressive early control and for detecting diabetes earlier. Mechanistically, the persistence of risk after the metabolic stimulus is withdrawn is difficult to explain without a heritable cellular memory, and the epigenetic marks described above are currently the best-supported candidate. This makes chromatin-modifying enzymes and the ncRNAs that direct them plausible therapeutic targets for patients whose glycemic control has already been optimized and who nonetheless continue to progress, a group for whom no mechanism-directed option currently exists.

Gut microbiota and the retina

Interest in the gut-retina axis follows from the broader recognition that intestinal microbial communities modulate systemic metabolism and immunity [25]. In diabetes, the gut microbiome composition shifts toward depletion of Bifidobacterium and Lactobacillus species and expansion of opportunistic Gram-negative organisms. This is accompanied by loss of intestinal barrier integrity, translocation of lipopolysaccharide into the portal and systemic circulation, and low-grade endotoxemia that engages Toll-like receptor 4 signaling in vascular and immune cells [20, 26]. Circulating inflammatory tone established in this way plausibly lowers the threshold for retinal inflammatory injury, although direct causal evidence in DR remains limited to rodent studies.

The metabolite arm of the axis is better characterized. Short-chain fatty acids (SCFAs), principally acetate, propionate, and butyrate, are generated by bacterial fermentation of dietary fiber and act both as energy substrates and as signaling molecules through free fatty acid receptors and inhibition of histone deacetylases [27]. Butyrate strengthens epithelial tight junctions and promotes regulatory T-cell differentiation, and its depletion in type 2 diabetes has been documented consistently [26]. This connects the microbiome directly to the epigenetic mechanisms discussed above, since histone deacetylase inhibition is one of the routes by which metabolic state is written into chromatin. Whether dietary fiber supplementation, defined probiotic consortia, or fecal microbiota transfer can shift retinal outcomes in patients is untested, and the field currently rests on associative human data plus interventional rodent data.

iPSC-derived retinal organoids and gene editing

Model systems have limited DR research more than most investigators acknowledge. Streptozotocin-treated rodents and db/db mice reproduce pericyte loss, acellular capillaries, and barrier breakdown, but do not develop preretinal neovascularization or tractional detachment, so the entire proliferative phase of human disease has no faithful small-animal counterpart. Oxygen-induced retinopathy models generate neovascularization but in a neonatal, non-diabetic context. Immortalized cell lines lack the architecture in which the NVU operates.

Human induced pluripotent stem cell (iPSC)-derived retinal organoids partially address this. These three-dimensional cultures self-organize into a laminated structure containing photoreceptors, bipolar cells, RGCs, and Müller glia, and reproduce key aspects of human retinogenesis including the epigenetic memory of the somatic cell of origin [28, 29]. Applied to diabetes, organoids exposed to high glucose or to combined metabolic stressors reproduce photoreceptor and RGC injury, Müller gliosis, and inflammatory activation at a stage corresponding to early clinical DR [30, 31]. Their principal limitation is the absence of vasculature and of circulating immune cells, meaning that barrier breakdown-the defining lesion of DR-cannot be modeled directly. Assembloid and microfluidic approaches incorporating endothelial and mural cells represent a logical next step. Species-adapted platforms offer a complementary

route: porcine iPSC-derived organoids exploit the structural similarity of the porcine retina to the human retina, including a cone-rich central region, and mature on a faster developmental timeline than their human counterparts [32]. Endogenous human retinal stem cell populations capable of regenerating retinal tissue have also been identified, which may eventually provide autologous material for both modeling and repair [33].

Combining organoids with CRISPR/Cas9 editing converts a descriptive model into an inferential one. Isogenic pairs differing only at a defined locus allow phenotypes such as junctional protein loss, cytokine release, or photoreceptor stress to be attributed causally to that locus rather than to line-to-line variation. The same editing tools can be applied in vivo: targeted disruption of Pik3cd in a murine model reduced pathological retinal angiogenesis without impairing physiological vessel development, illustrating the level of specificity now achievable [34]. For translational purposes, however, gene editing in the retina raises problems that organoid work does not solve, including delivery to postmitotic cells, mosaicism, and the impossibility of withdrawing treatment if an off-target effect emerges.

High-throughput screening as a gateway to preclinical development

Screening platforms determine which molecules ever reach animal testing. In vitro systems are attractive here because they are standardized, scalable, and inexpensive relative to in vivo work, and because they permit parallel assessment of efficacy and cytotoxicity across large compound sets [35]. For posterior-segment indications, screens increasingly evaluate not only the active molecule but also the carrier, since nanocarrier composition determines whether a compound reaches the retina at all [36].

Two examples illustrate the range of approaches. Structure-based virtual screening against the RNA-binding protein HuR, which stabilizes VEGF and tumor necrosis factor-alpha transcripts, identified indole derivatives that disrupt the HuR-mRNA complex and reduced VEGF and inflammatory mediator release from retinal endothelial cells under high-glucose conditions [37]. Phenotypic screening in retinal pigment epithelium (RPE) cells exposed to physiological stressors has similarly been used to identify cytoprotective compounds, although that work was framed around AMD rather than DR [38]. A third strategy starts from transcriptomic data rather than compound libraries. For example, integrated analysis of high-throughput sequencing datasets from PDR implicated CACNA1A as a mediator of VEGF expression and identified HNF4A as an upstream regulator acting through the CACNA1A/VEGF axis [39].

These platforms shorten the discovery phase and reduce animal use, but they also introduce a characteristic failure mode. Compounds selected for potency in a monolayer under acute high-glucose exposure are selected against exactly the properties that matter in vivo, namely persistence in the vitreous, penetration of the internal limiting membrane, and activity in a chronically rather than acutely stressed tissue. Screening cascades that incorporate an organoid or explant tier before animal work, and that measure carrier behavior alongside target engagement, are more likely to identify candidates that survive the transition.

Novel therapeutic targets in diabetic retinopathy

Anti-VEGF therapy became the reference standard for center-involving DME because VEGF-A is a direct driver of both vascular permeability and pathological angiogenesis, and because blocking it produces rapid, measurable anatomical improvement. Its limitations, however, are quantifiable, and it is worth stating them precisely because the figure most often quoted in the literature is applied more loosely than the underlying data support.

For DME, the most informative evidence comes from the DRCR Retina Network comparative effectiveness trials. In a secondary analysis of Protocol T, in which eyes received monthly aflibercept, bevacizumab, or ranibizumab, persistent central-involved macular thickening was still present after 24 weeks of continuous treatment in roughly one third to two fifths of eyes, with the proportion differing significantly by agent and lowest with aflibercept [5]. Comparable estimates emerge from the RISE and RIDE program, in which a majority of ranibizumab-treated eyes failed to achieve a 15-letter gain at 24 months despite monthly injection

[40]. Reviews of DME management accordingly describe an incomplete-response rate of approximately 30-40% [6]. Two qualifications matter. First, this range refers to anatomical non-resolution of edema, not to absence of any benefit; most such eyes still improve relative to baseline. Second, the range is derived from DME cohorts and should not be transferred to PDR. In PDR the relevant outcome is regression and non-recurrence of neovascularization, and in Protocol S ranibizumab was non-inferior to panretinal photocoagulation (PRP) over two years, with treatment failure manifesting mainly as recurrent neovascularization or vitreous hemorrhage in eyes that discontinued injections rather than as a fixed proportion of primary non-responders [41]. Throughout this review we therefore use "anti-VEGF therapy" to denote the treatment modality and "anti-VEGF agent" to denote a specific molecule, and we restrict the 30-40% figure to DME.

Incomplete response has several non-exclusive explanations: VEGF-independent drivers of permeability such as angiopoietin-2 (Ang2) and inflammatory cytokines; chronic edema with established Müller cell dysfunction and photoreceptor loss, in which fluid resolution cannot restore function; pharmacokinetic undertreatment because monthly dosing is not sustained outside trials; and, less commonly, tachyphylaxis. Each explanation points toward a different alternative target, which is the organizing logic of the sections that follow. **Table 1** summarizes these targets together with the level of evidence available in DR, the translational stage each has reached, and its principal limitation.

Inflammation and immunity

Chronic low-grade inflammation is now regarded as a driver rather than a consequence of DR progression. The NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome is activated in retinal cells by hyperglycemia-associated stimuli including reactive oxygen species, extracellular ATP, and AGEs, and its assembly leads to caspase-1-dependent maturation of interleukin-1 beta (IL-1β) and IL-18 and to gasdermin D-mediated pyroptosis of endothelial cells and pericytes [42]. Pharmacological and genetic inhibition of NLRP3 reduces vascular leakage and cell death in diabetic rodents, and several small-molecule NLRP3 inhibitors developed for systemic indications are being considered for ocular repurposing [43].

Upstream and in parallel, nuclear factor kappa-B (NF-κB) coordinates transcription of inflammatory and matrix-remodeling genes, including matrix metalloproteinase-9 (MMP-9), which contributes to mitochondrial damage and capillary cell apoptosis [44]. Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling transduces cytokine input into the same transcriptional program and has attracted attention because JAK inhibitors are already approved for systemic inflammatory disease [45]. Downstream, leukostasis provides a mechanical link between inflammation and ischemia: hyperglycemia upregulates intercellular adhesion molecule-1 (ICAM-1) on retinal endothelium, and meta-analysis confirms that circulating and intraocular ICAM-1 concentrations are elevated in patients with DR and rise with severity [46]. Adherent leukocytes plug capillaries, producing focal non-perfusion that itself increases VEGF expression.

The translational status of this target class is intermediate. Corticosteroids, which act broadly across these pathways, are already in clinical use and provide proof of principle that anti-inflammatory treatment benefits DME. Pathway-selective agents have not yet been tested in adequately powered DR trials, and the experience with systemic anti-inflammatory therapy in diabetes suggests that benefit may be confined to patients with a demonstrable inflammatory phenotype. This argues for biomarker-stratified rather than unselected trial designs.

Neuroprotection and metabolic correction

If neurodegeneration precedes clinically detectable vascular disease, then neuroprotection offers an opportunity to intervene earlier than any current treatment allows. Neurotrophic support of the inner retina depends on ciliary neurotrophic factor (CNTF), brain-derived neurotrophic factor (BDNF), and pigment epithelium-derived factor (PEDF), the last of which is also a potent endogenous anti-angiogenic

Table 1. Major therapeutic targets in diabetic retinopathy: evidence level and translational status

Target or pathway	Evidence level in DR	Translational stage	Representative agent(s)	Principal limitation
VEGF-A/VEGFR	High; multiple phase III RCTs	Approved	Ranibizumab, aflibercept, bevacizumab	Approximately 30-40% of DME eyes retain central macular thickening after 24 weeks of monthly therapy [5, 6]; in PDR the limitation is recurrence after interruption rather than primary non-response [41]; injection burden
VEGF-A + Ang2 (bispecific)	High; phase III RCTs in DME (YOSEMITE, RHINE)	Approved for DME	Faricimab	Benefit is principally extended durability rather than greater peak efficacy; long-term data still accruing [55]
Inflammation (NLRP3, NF-κB, JAK/STAT, ICAM-1)	Moderate; extensive preclinical, human biomarker association	Preclinical to phase I/II	NLRP3 inhibitors, JAK inhibitors, tocilizumab (IL-6R)	No pathway-selective agent approved for DR; broad-acting corticosteroids are the only clinical proof of principle; likely requires inflammatory-phenotype enrichment
Neuroprotection (BDNF, CNTF, PEDF, brimonidine, somatostatin)	Moderate; strong preclinical, one completed RCT with negative primary endpoint	Phase II	Topical brimonidine and somatostatin (EUROCONDOR); PEDF gene transfer	EUROCONDOR did not meet its primary endpoint in the overall cohort [49]; delivered retinal dose unquantified; functional endpoints not standardized
Metabolic correction (AMPK, SIRT1, lipid pathways)	Moderate to high for fenofibrate; low for others	Approved systemically (fenofibrate); preclinical for others	Fenofibrate; AMPK and SIRT1 activators	Mechanism of fenofibrate benefit incompletely defined; retinal selectivity of nutrient-sensing agents unproven
Complement (C3, C5a, MAC)	Low in DR; clinical proof of concept only in geographic atrophy	Preclinical in DR	Pegcetacoplan (approved for GA, not DR)	No genetic anchor in DR comparable with CFH/C3/CFB in AMD; younger population implies decades of exposure; infection risk; see **Table 4** [53]
ncRNAs (miRNA, lncRNA, circRNA)	Moderate as biomarkers; low to moderate as targets	Preclinical	Anti-MALAT1, anti-MIAT, anti-circZNF532, miR-200b mimic	Cell-type-specific retinal delivery unresolved; durability after single dose unreported; innate immune activation rarely controlled for; see **Table 3**

Abbreviations: DR, diabetic retinopathy; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; RCT, randomized controlled trial; DME, diabetic macular edema; PDR, proliferative diabetic retinopathy; Ang2, angiopoietin-2; NLRP3, nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3; NF-κB, nuclear factor kappa-B; JAK/STAT, Janus kinase/signal transducer and activator of transcription; ICAM-1, intercellular adhesion molecule-1; IL-6R, interleukin-6 receptor; BDNF, brain-derived neurotrophic factor; CNTF, ciliary neurotrophic factor; PEDF, pigment epithelium-derived factor; AMPK, adenosine monophosphate-activated protein kinase; SIRT1, sirtuin 1; MAC, membrane attack complex; GA, geographic atrophy; AMD, age-related macular degeneration; CFH, complement factor H; CFB, complement factor B; ncRNA, non-coding RNA; miRNA, microRNA; lncRNA, long non-coding RNA; circRNA, circular RNA. Evidence levels: High, phase III randomized trial data in DR; Moderate, phase I/II data or strong preclinical evidence in DR; Low, preclinical evidence in DR only.

protein acting through several identified receptors [47]. Retinal PEDF concentrations fall as DR progresses, inverting the PEDF/VEGF ratio, and restoring that ratio in animal models limits both neuronal loss and neovascularization [14, 47]. Redox signaling links this axis back to metabolism, since the enzymatic machinery generating and detoxifying reactive oxygen species also governs the survival signaling of retinal neurons [48].

The clinical experience here is instructive and deserves explicit mention, as it illustrates a recurring pattern in DR translation. The EUROCONDOR trial randomized patients with type 2 diabetes and early retinal changes to topical brimonidine, somatostatin, or placebo for two years. Neither active agent slowed progression of the primary neurodysfunction endpoint in the cohort as a whole, although a prespecified subgroup with pre-existing neurodysfunction at baseline showed a signal favoring treatment [49]. The trial did not disprove the neuroprotection hypothesis so much as demonstrate that patient selection, route of administration, and endpoint choice determine whether such a hypothesis can be adequately tested. Subsequent programs have accordingly emphasized enrichment strategies and functional endpoints such as multifocal electroretinography and microperimetry rather than photographic grading alone.

Metabolic correction operates on the same tissue from a different angle. Adenosine monophosphate-activated protein kinase (AMPK) and sirtuin 1 (SIRT1) activation restore autophagic flux and mitochondrial biogenesis in retinal cells under nutrient stress, and nutrient-sensing pathways are increasingly viewed as a unifying node across diabetic complications [50]. Systemically, fenofibrate reduced the need for laser treatment in the FIELD and ACCORD-Eye studies through mechanisms that appear only partly lipid-dependent, and retinal lipid handling is now recognized as a discrete pathogenic axis rather than a systemic epiphenomenon [51]. Fenofibrate is, at present, the clearest example in DR of a metabolic agent with randomized evidence of retinal benefit, and its mechanism remains incompletely explained, which is itself a reminder that mechanistic completeness is not a precondition for clinical utility.

Complement activation and the vascular microenvironment

Complement components are deposited in the retinal vasculature and choriocapillaris of donor eyes from diabetic patients, and complement regulators such as CD55 and CD59 are glycated and functionally impaired in hyperglycemia, which permits inappropriate assembly of the membrane attack complex (MAC) on host cells. The anaphylatoxins C3a and C5a recruit leukocytes and increase permeability, while sublytic MAC deposition on endothelial cells promotes a prothrombotic phenotype [52]. Preclinical complement inhibition reduces acellular capillary formation and leakage, which supports the pathway as a target.

Extrapolation from AMD requires caution here, and we state the limits explicitly. The complement hypothesis in AMD rests on genetic association data far stronger than any counterpart in DR: common variants in CFH, C3, and CFB confer large, replicated effects on AMD risk, and it was this genetic anchor that justified the clinical development of pegcetacoplan and avacincaptad pegol for geographic atrophy [53]. No comparable complement-gene association has been established for DR. The two diseases also differ in the compartment involved, with AMD pathology centered on the outer retina, RPE, and choriocapillaris and DR pathology centered on the inner retinal microvasculature; in the driver, with DR driven by a modifiable systemic metabolic derangement; in patient age, with DR affecting a population several decades younger; and consequently in expected treatment duration, since a DR patient starting complement inhibition in their fifth decade could require several decades of therapy. Long-term complement suppression carries an infection risk and, the geographic atrophy program was associated with an increased incidence of exudative conversion. Applying these agents to DR therefore requires dedicated DR studies with their own dose-finding and safety monitoring, not inference from AMD outcomes.

A more securely DR-anchored target within the same microenvironment is the angiopoietin/Tie2 axis, which governs pericyte-endothelial crosstalk and vascular stability. Ang2 antagonizes Tie2 signaling, destabilizes junctions, and sensitizes the endothelium to VEGF and to inflammatory mediators [54]. Simultaneous

neutralization of VEGF-A and Ang2 by the bispecific antibody faricimab produced non-inferior vision outcomes with extended dosing intervals in the YOSEMITE and RHINE trials in DME, providing the first registrational evidence that engaging a second, non-VEGF pathway improves durability rather than peak efficacy [55]. That distinction, durability versus efficacy, is worth keeping in view when evaluating other multi-target proposals.

Non-coding RNAs as candidate targets

Non-coding RNAs regulate essentially every process implicated in DR, including angiogenesis, apoptosis, inflammation, and epigenetic memory, and they do so combinatorially rather than through single-target relationships [56]. Three classes have received most attention.

MicroRNAs (miRNAs) are short regulatory transcripts that repress translation of target messenger RNAs. In DR, miR-200b directly targets VEGFA, and its downregulation in diabetic retina permits VEGF accumulation, while restoration of miR-200b reduces permeability in animal models [57]. Members of the miR-200 family also act through the transforming growth factor-beta 2/Smad axis to limit proliferation and apoptosis of retinal cells [58]. Polymorphisms in the genes encoding miR-155 and miR-146a associate with type 1 diabetes risk, linking the inflammatory arm of miRNA biology to disease susceptibility [59]. Because a single miRNA regulates hundreds of transcripts, miRNA-based therapy is intrinsically multi-target, which is an advantage for a polygenic process and a liability for safety [60].

lncRNAs act as scaffolds, chromatin regulators, and competing endogenous RNAs (ceRNAs) that sequester miRNAs [61]. Expression profiling of early diabetic retina identified widespread lncRNA dysregulation before overt vascular lesions appear [62]. MALAT1 is the best characterized: it is upregulated in diabetic retina and in high-glucose-treated endothelial cells, and its knockdown reduces endothelial proliferation, migration, and inflammation [63]. In diabetic mice, targeting MALAT1 alleviated retinal neurodegeneration [64], and MALAT1 promotes angiogenesis through a miR-320a/hypoxia-inducible factor-1 alpha axis [65]. Circulating lncRNAs additionally correlate with insulin resistance, senescence, and inflammation in type 2 diabetes, suggesting a dual role as both biomarkers and functional effectors [66]. MIAT is a second well-supported example, promoting endothelial dysfunction, apoptosis, and pyroptosis partly by sponging miR-29b [67].

Circular RNAs (circRNAs) are covalently closed transcripts whose resistance to exonuclease degradation gives them unusual stability in tissue and in body fluids [68]. cPWWP2A and circRNA-MET modulate pericyte and endothelial tip-cell behavior respectively, and silencing circRNA-MET inhibits pathological angiogenesis without affecting normal vessels [69]. circZNF532 regulates diabetic pericyte degeneration through a miR-29a-3p/NG2-LOXL2-CDK2 network, and its knockdown reproduces the pericyte phenotype of diabetes [70]. Several circRNAs also act through PI3K/AKT signaling [71], and profiling studies have proposed circRNA panels in aqueous humor and plasma as diagnostic markers [72]. Beyond sponging, circRNAs participate in chromatin regulation and macrophage metabolic reprogramming, and a subset is translated into functional peptides, an activity that dedicated bioinformatic resources are now able to predict [73-75].

A distinction that the ncRNA literature in DR often blurs is worth making explicit, because it determines what evidence each candidate requires. Using an ncRNA as a biomarker requires only that its abundance in an accessible compartment track disease state reproducibly across independent cohorts; causality is irrelevant, and circRNAs are particularly well suited to this role because their stability survives sample handling [68, 72]. Using an ncRNA as a therapeutic target requires considerably more: evidence that it is causally upstream of a pathogenic process rather than a marker of it, that modulating it in the relevant cell type changes the phenotype, that the change is durable, and that the many other transcripts the ncRNA regulates can be perturbed without unacceptable consequence. Most published DR studies establish differential expression and a cell-culture phenotype, which supports the first application and only partially supports the second. Where in vivo work exists, as for MALAT1 [64], circRNA-MET [69], and circZNF532 [70], it typically uses intravitreal injection of an antagomir or short hairpin construct

in a rodent model over a few weeks, which demonstrates biological plausibility without addressing durability, cell selectivity, or the innate immune considerations discussed in Section 3.2.

The volume of this literature contrasts sharply with its translational output, and Section 3.2 addresses the reasons directly rather than restating them as a generic call for further study.

Preclinical development: molecules, delivery systems, and strategies

Next-generation anti-VEGF agents and other protein therapeutics

Efforts to improve on current anti-VEGF therapy have followed three distinct engineering strategies, and it is useful to separate them because they solve different problems. The first increases the delivered dose. High-molar-concentration formulations extend the interval over which intravitreal drug concentration remains above the threshold for VEGF suppression, and aflibercept reformulated at 8 mg has been evaluated in DME with extended dosing intervals on this rationale. The second increases intrinsic potency or tissue penetration. Brolucizumab is a single-chain variable fragment of approximately 26 kDa whose small size permits a much higher molar dose in the same injection volume and improves diffusion into the outer retina; in the HAWK and HARRIER trials in neovascular AMD it achieved greater fluid resolution than aflibercept at matched or extended intervals [76]. The third broadens pathway coverage, exemplified by the bispecific VEGF-A/Ang2 antibody faricimab discussed above and confirmed in DME by YOSEMITE and RHINE [55], and supported indirectly by network meta-analyses comparing the available agents [77].

Brolucizumab also provides an important safety lesson that qualifies the first two strategies. Post-marketing surveillance and post hoc review of HAWK and HARRIER identified intraocular inflammation, retinal vasculitis, and retinal vascular occlusion at rates exceeding those of comparator agents, an event cluster that appears related to immunogenicity of the small antibody fragment [78]. The relevance to DR is direct: the diabetic eye already carries an activated inflammatory and prothrombotic microenvironment, so an agent whose principal risk is inflammatory occlusive vasculopathy cannot be assumed to have the same benefit-risk profile in DR as in AMD. This is one of several instances in which AMD-derived efficacy data and AMD-derived safety data must be evaluated separately before being applied to DR.

Beyond VEGF, protein therapeutics directed at individual mediators have entered early clinical evaluation. IL-6 receptor blockade with tocilizumab is rationalized by elevated intraocular IL-6 concentrations in refractory DME and by the established efficacy of IL-6 blockade in non-infectious uveitic macular edema [79]. Complement inhibitors such as pegcetacoplan have registrational data only in geographic atrophy [53], and the constraints on transferring that evidence to DR are set out in Section 2.3 and assessed in detail in Section 4.4. An unconventional protein-directed approach is active rather than passive immunization: a messenger RNA vaccine encoding the pro-angiogenic protein LRG1, given intramuscularly, elicited neutralizing antibodies and reduced retinal leakage and lesion size in animal models of choroidal neovascularization to a degree comparable with anti-VEGF agents, without intraocular injection [80]. The concept is attractive for a chronic disease requiring lifelong treatment, but a systemically induced, long-lived antibody response cannot be withdrawn if adverse effects appear, and LRG1 has physiological roles outside the eye; both considerations weigh more heavily in a younger DR population than in elderly AMD cohorts.

Nucleic acid therapeutics: delivery bottlenecks and lessons from failed trials

Nucleic acid therapeutics offer the most direct route to the ncRNA targets described in Section 2.4. siRNA, antisense oligonucleotides (ASOs), miRNA mimics, and anti-miRs act at the transcript level and can, in principle, address targets that are undruggable with small molecules or antibodies. Proof of concept in the diabetic retina exists: intravitreal delivery of HuR-targeting siRNA formulated in liposome-polyethylenimine lipopolyplexes reduced retinal HuR and VEGF expression in diabetic rats [81] (**Table 2**), and ASO chemistry has been evaluated in DR since the late 2000s [82]. What the

Table 2. Advanced drug delivery systems for diabetic retinopathy evaluated in preclinical studies

Platform	Payload	Model and route	Principal preclinical finding	Translational limitation
Liposome-polyethylenimine lipopolyplex	HuR-targeting siRNA	Diabetic rat; intravitreal	Reduced retinal HuR and VEGF expression [81]	Cationic complexes aggregate in vitreous; cell-type selectivity not demonstrated; duration of silencing not reported
Hybrid erythrocyte-endothelial membrane-coated nanoparticle	Anti-angiogenic small molecule	Diabetic rat; intravenous	Selective homing to retinal vasculature with reduced VEGF and leakage, no systemic toxicity [95]	Systemic dosing raises whole-body exposure; membrane sourcing and batch consistency unresolved for manufacture
PLGA microspheres	Full-length bevacizumab	In vitro release and intraocular models	Extended antibody release with retained binding activity, supporting multi-month dosing [96]	Release characterized in normal, not diabetic or vitrectomized, vitreous; protein aggregation over time
Thermosensitive hydrogel composite	Connexin-43 siRNA nanoparticles plus anti-VEGF agent	Diabetic animal model; intravitreal	Synergistic reduction of neovascularization and leakage from a single injectable depot [97]	Gel residence and degradation products in the human eye uncharacterized; combination adds regulatory complexity
Metal, liposomal, and chitosan nanocarriers	Various anti-inflammatory and anti-angiogenic agents	Multiple rodent models; intravitreal and topical	Improved ocular bioavailability and residence time relative to free drug [93]	Heterogeneous methods preclude cross-study comparison; long-term retinal tolerability of metal cores unresolved
Long-acting nanotherapeutic for minimally invasive administration	Anti-angiogenic payload	Neovascular retinal disease model	Sustained release with reduced administration frequency [98]	Developed in an AMD model; efficacy in the diabetic microenvironment not established
Dissolving microneedle array	Dexamethasone-loaded microparticles	Ex vivo sclera; transscleral	Microparticle deposition within sclera with sustained transscleral flux [102]	Choroidal clearance and RPE barrier limit retinal delivery; ex vivo model excludes blood flow
Intranasal formulation	Erythropoietin	Degenerative retina model; intranasal	Photoreceptor rescue after non-invasive administration [103]	Delivered retinal concentration not quantified; nasal absorption variability between subjects
Engineered AAV capsid	Anti-VEGF transgene	Non-human primate and rodent; intravitreal	Inner retinal transduction after intravitreal rather than subretinal injection [85, 86]	Vector immunogenicity; expression cannot be titrated or withdrawn
Refillable ocular implant (device)	Ranibizumab	Randomized phase III, neovascular AMD	Six-month refill interval with non-inferior acuity outcomes [99]	Endophthalmitis and conjunctival erosion risk; requires surgical implantation; DR-specific data still limited

Abbreviations: siRNA, small interfering RNA; VEGF, vascular endothelial growth factor; PLGA, poly (lactic-co-glycolic acid); RPE, retinal pigment epithelium; AAV, adeno-associated virus; AMD, age-related macular degeneration; DR, diabetic retinopathy.

field has not yet produced is an approved ocular nucleic acid drug for DR, and the reasons are specific enough to be enumerated.

The first and most consequential bottleneck is cell-type-specific delivery. Naked oligonucleotides injected into the vitreous face a dense, negatively charged network of hyaluronan and collagen fibrils that immobilizes cationic complexes through electrostatic aggregation, followed by the internal limiting membrane, which excludes particles above roughly 100 nm. Material that does reach the retina distributes preferentially to Müller glia and RPE, whereas the cells of interest in DR are endothelial cells and pericytes. The comparison with hepatic RNAi is instructive. Systemic siRNA therapy became viable once two delivery problems were solved: ionizable lipid nanoparticles (LNPs) provided endosomal escape and enabled the first approved RNAi drug, and N-acetylgalactosamine (GalNAc) conjugation subsequently provided receptor-mediated, hepatocyte-restricted uptake through the asialoglycoprotein receptor, removing the need for a carrier altogether [83, 84]. This success has not translated to the retina for biological rather than chemical reasons: the asialoglycoprotein receptor is expressed at extraordinarily high density and near-exclusively on hepatocytes, and no retinal cell type has a validated equivalent. Candidate ligands under investigation include integrin-binding RGD peptides and transferrin receptor ligands for endothelium and mannose receptor ligands for microglia, but none has yet demonstrated the combination of density, selectivity, and internalization efficiency that makes GalNAc work. Until such a ligand is identified, cell-type specificity in the retina will have to be achieved through carrier engineering, promoter selection, or capsid engineering rather than through conjugate chemistry.

LNPs themselves have been adapted for ocular use with partial success. Neutral or anionic surface charge and dense polyethylene glycol coating improve mobility through vitreous, and subretinal administration bypasses the vitreous entirely and delivers efficiently to RPE and photoreceptors, but subretinal injection is a surgical procedure that is difficult to justify for a chronic, bilateral, and initially asymptomatic disease. LNP-associated innate immune activation, tolerable for a single vaccine dose, is a more serious concern under repeated intraocular administration [83]. Viral vectors are the established alternative, and directed evolution of adeno-associated virus capsids has produced variants capable of transducing inner retinal cells after intravitreal rather than subretinal injection [85], with preclinical gene-therapy constructs expressing anti-VEGF proteins after a single administration [86]. Vector immunogenicity, the irreversibility of expression, and the difficulty of dose titration remain unresolved. Extracellular vesicles offer a third route that avoids both synthetic lipids and viral capsids, since exosomes derived from mesenchymal stromal or retinal cells naturally traffic ncRNA cargo between retinal cell types and have been proposed as carriers for therapeutic ncRNA in DR [87]; their limitation at present is manufacturing reproducibility and the difficulty of loading a defined dose.

The second bottleneck is stability and specificity. Unmodified siRNA is degraded within hours in vitreous, so sustained silencing requires either chemical modification, 2’-O-methyl and 2’-fluoro substitutions and phosphorothioate backbones being standard, or embedding within a depot. Chemical modification serves a second purpose, which is to reduce recognition by innate immune sensors, and this brings us to the most important cautionary episode in the field.

Bevasiranib, an unmodified siRNA targeting VEGFA, entered phase III development for neovascular AMD on the strength of preclinical efficacy and early clinical data, and the COBALT trial was terminated at interim analysis when the primary visual acuity endpoint was unlikely to be met [88]. In parallel, work published in 2008 demonstrated that intravitreal siRNA of 21 nucleotides or longer suppressed choroidal neovascularization in a sequence-independent manner, including siRNAs targeting irrelevant genes, via TLR-3 signaling on endothelium and consequent IFN-γ and IL-12 release [89]. The anti-angiogenic effect attributed to target silencing was therefore, at least in substantial part, a class effect of double-stranded RNA acting as an innate immune ligand. The lesson is methodological rather than chemical: the preclinical program lacked control experiments, in particular scrambled and mismatched sequences and target-knockout animals,

that would have distinguished on-target from off-target activity.

Subsequent ophthalmic nucleic acid programs did not fully absorb this lesson. PF-04523655, a chemically modified siRNA targeting the hypoxia-inducible gene RTP801, was tested in DME in the DEGAS study, where it did not demonstrate superiority over laser at the primary timepoint despite a dose-response signal, and in neovascular AMD in the MONET study, where combination with ranibizumab did not clearly improve on ranibizumab alone [90, 91]. iCo-007, an ASO against c-Raf kinase, showed acceptable safety in DME but did not establish a monotherapy benefit [82]. Even the aptamer pegaptanib, which reached approval for AMD and showed activity in DME in phase II, was rapidly displaced by full-length and fusion anti-VEGF proteins because partial VEGF-isoform blockade proved less effective than pan-VEGF-A blockade [92]. Taken together, these programs indicate three recurring errors: reliance on efficacy readouts that innate immune activation can mimic; comparators and endpoints chosen before the delivery problem was solved, so that negative results are uninterpretable as tests of the biological hypothesis; and progression to phase III without pharmacodynamic evidence of target engagement in the intended cell type. **Table 3** summarizes these programs and the specific control experiment or design feature that was absent.

Applied to the current generation of ncRNA candidates, these lessons imply a concrete and fairly demanding checklist. Any anti-MALAT1, anti-MIAT, anti-circZNF532, or miR-200b-mimic program intending clinical development should demonstrate silencing in the specific retinal cell population implicated, using sequence-matched inert controls in an animal model of diabetes rather than of oxygen-induced retinopathy; it should establish the duration of silencing after a single administration, since an agent requiring monthly injections would offer little advantage over existing anti-VEGF therapy; it should quantify innate immune activation directly; and it should define a pharmacodynamic biomarker measurable in aqueous humor to permit dose selection before efficacy trials begin. Very few published ncRNA studies in DR currently meet more than one of these criteria, which is the honest characterization of the field's translational readiness.

Nanocarriers and long-acting release systems

Delivery constraints have rendered carrier design as critical as molecular design. Polymeric nanoparticles, particularly those based on poly (lactic-co-glycolic acid) (PLGA), protect labile payloads, permit surface functionalization with targeting ligands, and degrade into non-toxic monomers; liposomes and metal- or chitosan-based nanocarriers offer complementary loading characteristics for hydrophilic and hydrophobic agents [93, 94]. Biomimetic surface engineering is a more recent development with direct DR relevance: nanoparticles coated with a hybrid membrane derived from erythrocytes and endothelial cells, given intravenously, homed to inflamed retinal vasculature in diabetic rats, reduced VEGF expression and vascular leakage, and did so without detectable systemic toxicity [95]. The significance of that study is that it achieved retinal targeting from a systemic route, which if reproducible would remove the injection burden entirely.

For durability, the field has moved toward depot-forming systems. PLGA microspheres loaded with full-length bevacizumab released antibody over an extended period in vitro with retention of binding activity, supporting a multi-month dosing interval in principle [96]. Thermosensitive hydrogels provide an alternative depot that is liquid on injection and gels at body temperature; a composite hydrogel co-delivering connexin-43-targeting siRNA nanoparticles and an anti-VEGF agent produced synergistic effects in diabetic animals, and is notable as one of the few systems that combines a nucleic acid and a protein therapeutic in a single sustained-release vehicle [97]. Long-acting nanotherapeutics designed for minimally invasive administration have shown extended release in neovascular retinal disease models [98]. The device-based analogue - the refillable port delivery system with ranibizumab - achieved a six-month refill interval in a phase III trial for neovascular AMD [99]. A DME program followed, and the device experience is instructive because its principal difficulties (endophthalmitis risk and conjunctival erosion) were surgical rather than pharmacological. The broader class of long-acting intraocular injectables and implants has been reviewed elsewhere [100].

Two limitations recur across this literature and are visible in **Table 2**. Most studies report fol-

Table 3. Terminated or negative ocular nucleic acid therapeutic programs and the design features that were absent

Agent and class	Target	Indication and study	Outcome	Design feature absent or lesson
Bevasiranib; unmodified siRNA	VEGFA	Neovascular AMD; COBALT (phase III)	Terminated at interim analysis for unlikely benefit on visual acuity [88]	Preclinical program lacked sequence-mismatched controls; the anti-angiogenic effect of intravitreal siRNA was subsequently shown to be sequence-independent and mediated by cell-surface TLR3 [89]
PF-04523655; chemically modified siRNA	RTP801 (DDIT4)	DME; DEGAS (phase II)	Did not demonstrate superiority over laser at the primary timepoint despite a dose-response signal [90]	Target engagement in the intended retinal cell type was not demonstrated pharmacodynamically before efficacy testing
PF-04523655; chemically modified siRNA	RTP801 (DDIT4)	Neovascular AMD; MONET (phase II)	Combination with ranibizumab did not clearly improve on ranibizumab alone [91]	Add-on design against a highly effective comparator without a biomarker-enriched population
iCo-007; antisense oligonucleotide	c-Raf kinase	DME (phase II)	Acceptable safety; monotherapy benefit not established [82]	Duration of silencing after single intravitreal dose not characterized; monotherapy comparison chosen before delivery adequacy was confirmed
Pegaptanib; aptamer	VEGF-165 isoform	DME (phase II) and neovascular AMD (approved)	Active but displaced by pan-VEGF-A agents [92]	Partial isoform blockade proved insufficient; illustrates that target selectivity is not always advantageous

Abbreviations: siRNA, small interfering RNA; VEGFA, vascular endothelial growth factor A; AMD, age-related macular degeneration; DME, diabetic macular edema; TLR3, Toll-like receptor 3; RTP801/DDIT4, DNA damage-inducible transcript 4; VEGF, vascular endothelial growth factor.

low-up of weeks in animals with a disease duration of weeks, whereas human DR develops over decades, so neither carrier degradation kinetics nor the long-term tolerability of accumulated polymer has been established in a relevant timeframe. Plus the diabetic vitreous differs from the normal vitreous in viscosity, protein content, and oxidative state, particularly after vitrectomy, yet release kinetics are almost always characterized in normal vitreous or in buffer. Both gaps are addressable with existing methods and would materially improve the interpretability of preclinical delivery studies.

Alternative routes of administration

Reducing or eliminating intravitreal injection is a goal in its own right, since injection burden drives non-adherence and non-adherence is a stronger predictor of poor outcome in real-world DME cohorts than any pharmacological variable. Transscleral delivery exploits the large surface area and relative permeability of the sclera to macromolecules, with the choroidal circulation and the RPE barrier as the principal obstacles [101]. Dissolving microneedle arrays partially overcome these by depositing drug-loaded microparticles within the sclera itself, and such arrays have delivered dexamethasone microparticles across sclera in ex vivo models [102]. Suprachoroidal injection is the clinically furthest-advanced version of this concept and is now approved for uveitic macular edema, providing a route that concentrates drug at the chorioretinal interface while sparing the anterior segment.

Intranasal administration exploits olfactory and trigeminal pathways to reach the posterior eye while bypassing systemic circulation; intranasal erythropoietin rescued photoreceptors in a degenerative retinal model, establishing that a protein of that size can reach the retina by this route [103]. Topical delivery remains the most patient-acceptable option and the least efficient, with penetration to the posterior segment generally below one percent of the applied dose; the EUROCONDOR experience with topical neuroprotective agents illustrates the difficulty of demonstrating efficacy when the delivered dose at the target is unknown [49]. Across all of these routes, the recurring deficiency is quantitative: few studies report retinal drug concentrations over time, making it impossible to determine whether a negative efficacy result reflects an inactive molecule or inadequate delivery.

Clinical translation: diagnostics, combination regimens, and device-based therapy

Section 4 addresses what has actually reached patients. It is organized around three questions that clinical translation must answer in sequence: how disease is detected and stratified, how existing agents are combined and sequenced, and what non-pharmacological platforms can add. Preclinical material and prospective research priorities are treated in Sections 3 and 5 respectively, so that this section deals only with evidence generated in human subjects.

Molecular biomarkers and artificial intelligence (AI) in diagnosis and prognosis

Intraocular cytokine profiling provides the mechanistic layer of DR diagnostics. Aqueous humor concentrations of soluble VEGF receptors, placental growth factor, soluble platelet-derived growth factor-AA, IL-6, and monocyte chemoattractant protein-1 correlate with macular thickness and DME severity, and their relative pattern differs between eyes with predominantly angiogenic and predominantly inflammatory phenotypes [104]. This heterogeneity is clinically meaningful, since inflammation-dominant eyes respond better to corticosteroids and angiogenesis-dominant eyes to anti-VEGF therapy [105]. The obstacle to routine use is that aqueous sampling requires an anterior chamber tap, which is acceptable at the time of an injection but not as a screening procedure; tear-film and plasma surrogates, including circulating ncRNA panels [72], are being evaluated for this reason.

Image-based AI has translated considerably faster and currently represents one of the clearest examples of a DR technology that has completed the full bench-to-bedside path. A deep learning algorithm developed on approximately 128,000 fundus photographs achieved sensitivity and specificity above 90% for referable DR against a reference standard of ophthalmologist grading [106], and an autonomous system was subsequently evaluated in a prospective pivotal trial conducted in primary care

settings and became the first autonomous diagnostic device authorized in this field, meaning that it produces a screening result without physician interpretation [107]. Deep learning applied to optical coherence tomography and to ultra-widefield imaging extends the same approach to DME detection and to peripheral ischemia quantification [108].

Two qualifications should be noted regarding this success. First, performance degrades when algorithms are deployed in populations differing from the development set in camera type, image quality, or pigmentation, so external validation in the intended deployment setting is a requirement rather than a refinement. Second, screening is a substantially easier task than prognosis. Predicting which eyes will progress, and over what interval, requires longitudinal data and integration of systemic variables such as glycated hemoglobin trajectory, blood pressure, and renal function, and models of this kind are at an earlier stage. Combining molecular and imaging features in multimodal models is the natural next step and is where the cytokine work described above is most likely to find clinical application [75, 108].

Combination and sequential drug regimens

Combination therapy in DR is best understood as an attempt to address the incomplete-response problem quantified in Section 2. The most extensively studied combination pairs anti-VEGF therapy with intravitreal corticosteroid, on the rationale that the two act on partly non-overlapping mediators. In eyes with DME refractory to repeated anti-VEGF injection, adding a sustained-release dexamethasone implant reduces central retinal thickness and improves visual acuity. The most prominent effects are seen in eyes with imaging or biochemical markers of inflammation, such as hyperreflective foci or subretinal fluid [109]. The trade-off is predictable, since cataract progression and intraocular pressure elevation are dose-dependent and cumulative, which makes pseudophakic eyes the preferred candidates.

In PDR, the relevant combination is pharmacological and ablative rather than pharmacological alone. Comparative effectiveness data from large real-world cohorts indicate that eyes initially managed with anti-VEGF monotherapy have higher rates of subsequent vitrectomy and of vitreous hemorrhage than eyes receiving PRP, an outcome attributable largely to loss to follow-up, since neovascular regression achieved with injections reverses when injections stop whereas PRP effects persist [110]. This is a translational finding of a different kind, in that the limiting factor is health-system behavior rather than biology, and it argues for PRP or combined PRP-plus-injection strategies in patients whose adherence is uncertain.

Systemic risk-factor control remains the least glamorous and most reliably effective adjunct. Glycemic, blood pressure, and lipid management slow DR progression and reduce the frequency with which ocular treatment is required [111], and the interaction between systemic control and ocular treatment burden is a legitimate endpoint for future combination trials rather than a background variable to be adjusted away.

Sustained-release implants in clinical use

Two corticosteroid implants exemplify the achievements of sustained release in DR. The biodegradable dexamethasone intravitreal implant releases drug over approximately three to six months and improved visual acuity in a three-year randomized sham-controlled trial in DME [112]. The non-biodegradable fluocinolone acetonide insert releases a much lower daily dose over up to three years, with benefit sustained across that period and with the highest cataract and pressure-related event rates of the available options [113, 114]. The comparison between them is a useful reference point for any long-acting system: a shorter-acting, biodegradable device tolerates a higher peak dose and permits treatment withdrawal, whereas a multi-year device maximizes adherence benefit at the cost of reversibility. Anti-VEGF depot systems now in development face the same trade-off, and the port delivery system resolves it by remaining refillable and explantable [99].

Cell-based and device-based approaches: status and limits of extrapolation

Regenerative and prosthetic strategies are frequently cited in DR reviews on the basis of AMD data, and the transfer requires more scrutiny than it usually receives. In a clinical study of ten

patients with advanced neovascular AMD, a two-stage procedure combining surgical excision of the choroidal neovascular membrane with human embryonic stem cell-derived RPE transplantation produced improved retinal structure and stable or improved acuity over 12 months in patients with complete excision. Incomplete excision was followed by persistent inflammation and hemorrhage without visual gain [115]. Subretinal photovoltaic implantation restored a measurable degree of form vision in patients with geographic atrophy in a prospective multicenter trial [116].

Both results are genuine advances, and neither transfers directly to DR. RPE transplantation addresses a disease whose primary lesion is RPE atrophy; in DR the RPE is comparatively preserved and the primary lesion is inner retinal microvascular and neuronal, so replacing RPE would not address the pathology. Photovoltaic implants substitute for lost photoreceptors in a localized atrophic lesion within an otherwise structurally intact retina, whereas advanced PDR presents with tractional distortion, ischemia of the inner retina including the RGCs that carry the signal to the brain, and frequently a compromised optic nerve, all of which limit what a subretinal photoreceptor substitute can achieve. In addition, both procedures involve vitreoretinal surgery in eyes with impaired wound healing and elevated proliferative vitreoretinopathy risk, and both require immunological or long-term biocompatibility follow-up in a patient population that is younger and has a longer expected exposure. The appropriate conclusion is that these platforms establish surgical and manufacturing feasibility, but DR-specific application should be evaluated against DR-specific targets, plausibly endothelial or pericyte progenitor cells for vascular repair, rather than RPE replacement. **Table 4** sets out this analysis for each of the AMD-derived lines of evidence cited in this review.

Conclusions and future perspectives

The trajectory of DR translational research is shifting from single-target to multi-target intervention, and from reactive treatment of established vascular lesions to earlier intervention against the metabolic, inflammatory, and neurodegenerative processes that precede them. The mechanistic basis for this shift is secure. The clinical basis is narrower than the volume of publication suggests: outside anti-VEGF therapy, corticosteroids, laser, and fenofibrate, no agent has randomized evidence of benefit on visual outcomes in DR, and the one registrational advance beyond VEGF monotherapy, dual VEGF-A/Ang2 inhibition, improved durability rather than peak efficacy [55].

Four priorities follow from the analysis in this review. The first is delivery. For nucleic acid and gene-directed therapeutics, cell-type-specific delivery to retinal endothelium and pericytes remains the key unresolved problem on which clinical viability depends, and progress requires identification of a retinal receptor-ligand pair with the density and selectivity that GalNAc conjugation exploits in the liver, or capsid and promoter engineering that achieves equivalent restriction [84, 85]. Until then, ncRNA candidates should be evaluated in preclinical studies that report retinal concentration and cell-level target engagement, not only phenotypic endpoints.

The second is design discipline in early-phase work. The bevasiranib episode showed that an apparently robust preclinical effect can be an artifact of innate immune activation when sequence-matched controls are omitted [88, 89], and the DEGAS, MONET, and EUROCONDOR results showed that trials conducted before delivery and patient-selection problems are solved generate uninterpretable negative results rather than informative ones [49, 90, 91]. Enrichment by molecular or imaging phenotype, pharmacodynamic confirmation of target engagement, and functional endpoints such as microperimetry and multifocal electroretinography should be built into first-in-human design rather than added after a negative phase II.

Third, evidence from other retinal diseases should be treated as hypothesis-generating only. Complement inhibition, stem cell transplantation, and photovoltaic implantation have all been cited in DR reviews on the strength of AMD data, and each differs from DR in the compartment affected, the driver of pathology, the age and expected treatment duration of the patient, and, in the case of complement, in whether a genetic anchor for the target exists at all. We have set out these differences case by case in **Table 4**, and we conclude that each

Table 4. Assessment of evidence extrapolated from age-related macular degeneration to diabetic retinopathy

AMD-derived evidence cited in this review	Principal differences from DR	Consequence for extrapolation	DR-specific study required
Complement inhibition; pegcetacoplan in geographic atrophy [53]	Complement genetics (CFH, C3, CFB) provide a strong replicated risk anchor in AMD with no DR equivalent; outer retina/RPE/choriocapillaris versus inner retinal microvasculature; DR patients are several decades younger	Rationale in DR rests on descriptive deposition data alone; lifelong suppression implies far longer infection exposure	Complement activation profiling in DR ocular fluids by disease stage, followed by dedicated dose-finding and safety study in DR
Brolucizumab efficacy in HAWK and HARRIER [76]	The diabetic eye has a pre-activated inflammatory and prothrombotic microenvironment	Efficacy data may transfer; the inflammatory occlusive vasculopathy signal [78] may be amplified rather than reproduced in DR	Prospective safety evaluation in DME and PDR with predefined intraocular inflammation surveillance
Human embryonic stem cell-derived RPE transplantation [115]	Primary lesion in AMD is RPE atrophy; in DR the RPE is comparatively preserved and injury is inner retinal and microvascular	Replacing RPE does not address DR pathology; the procedure also carries higher proliferative vitreoretinopathy risk in diabetic eyes	If cell therapy is pursued in DR, the appropriate target is vascular repair using endothelial or pericyte progenitors, evaluated on perfusion endpoints
Subretinal photovoltaic implant in geographic atrophy [116]	Implants substitute for photoreceptors within an otherwise intact retina; advanced PDR involves inner retinal ischemia, RGC loss, traction, and optic nerve compromise	Signal generated by a photoreceptor substitute may not be transmitted in an eye with damaged inner retinal circuitry	Feasibility study restricted to PDR eyes with documented inner retinal and RGC integrity
LRG1 mRNA vaccine in choroidal neovascularization models [80]	Younger DR population with decades of expected exposure; systemic immunization affects LRG1 functions outside the eye	A durable systemic antibody response cannot be withdrawn if adverse effects emerge	Systemic safety and reversibility assessment plus DR model efficacy before clinical translation

Abbreviations: AMD, age-related macular degeneration; DR, diabetic retinopathy; RPE, retinal pigment epithelium; PDR, proliferative diabetic retinopathy; RGC, retinal ganglion cell; DME, diabetic macular edema; LRG1, leucine-rich alpha-2-glycoprotein 1; CFH, complement factor H; CFB, complement factor B.

of these strategies requires a DR-specific preclinical rationale and a DR-specific dose-finding and safety program before clinical adoption is considered. The general point applies beyond the examples discussed here: mechanistic analogy between retinal diseases is a reason to design a study, not a substitute for conducting one.

The fourth is infrastructure. Unified, DR-specific endpoints would allow multi-target trials to be compared directly, which is currently impossible when one program reports gain in visual acuity letters, another central subfield thickness, and a third change in DR severity score. Longer preclinical follow-up matched to the chronicity of human disease, characterization of drug release in diabetic and vitrectomized eyes, and reporting standards that require retinal pharmacokinetic data alongside efficacy data would collectively raise the proportion of preclinical findings that survive translation. None of these requires new technology.

In this respect, DR is a tractable challenge. The pathophysiology is better understood than that of most retinal diseases, the target tissue is accessible and directly imageable, and the patient population is identifiable years before vision is lost. What is missing is not mechanistic insight but the delivery technology, trial design, and endpoint infrastructure needed to convert that insight into treatment. Closing this gap will depend on sustained collaboration between retinal biologists, formulation scientists, clinical trialists, and the diabetes care teams who see these patients long before an ophthalmologist does.

Disclosure of conflict of interest

None.

Abbreviations

DR, Diabetic retinopathy; DM, diabetes mellitus; NVU, neurovascular unit; RGCs, retinal ganglion cells; AGEs, advanced glycation end-products; PKC, protein kinase C; SCFAs, short-chain fatty acids; iPSC, induced pluripotent stem cell; Ang2, Angiopoietin-2; VEGF, vascular endothelial growth factor; ncRNAs, Non-coding RNAs; miRNAs, microRNAs; lncRNAs, long non-coding RNAs; circRNAs, circular RNAs; ceRNAs, competing endogenous RNAs; siRNA, small interfering RNA; ASOs, antisense oligonucleotides; wAMD, wet age-related macular degeneration; AI, artificial intelligence; PDR, proliferative diabetic retinopathy; PRP, panretinal photocoagulation; DME, diabetic macular edema; NVU, neurovascular unit; RPE, retinal pigment epithelium; AMD, age-related macular degeneration; NLRP3, nucleotide-binding oligomerisation domain-like receptor family pyrin domain-containing 3; NF-κB, nuclear factor kappa-B; JAK/STAT, Janus kinase/signal transducer and activator of transcription; ICAM-1, intercellular adhesion molecule-1; IL, interleukin; BDNF, brain-derived neurotrophic factor; CNTF, ciliary neurotrophic factor; PEDF, pigment epithelium-derived factor; AMPK, adenosine monophosphate-activated protein kinase; SIRT1, sirtuin 1; MAC, membrane attack complex; PLGA, poly(lactic-co-glycolic acid); LNP, lipid nanoparticle; GalNAc, N-acetylgalactosamine; AAV, adeno-associated virus; CRISPR, clustered regularly interspaced short palindromic repeats; PRP, panretinal photocoagulation; RCT, randomised controlled trial.

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References

[1] Teo ZL, Tham YC, Yu M, Chee ML, Rim TH, Cheung N, Bikbov MM, Wang YX, Tang Y, Lu Y, Wong IY, Ting DSW, Tan GSW, Jonas JB, Sabanayagam C, Wong TY and Cheng CY. Global prevalence of diabetic retinopathy and projection of burden through 2045: systematic review and meta-analysis. Ophthalmology 2021; 128: 1580-1591.

[2] GBD 2019 Blindness and Vision Impairment Collaborators and Vision Loss Expert Group of the Global Burden of Disease Study. Causes of blindness and vision impairment in 2020 and trends over 30 years, and prevalence of avoidable blindness in relation to VISION 2020: the right to sight: an analysis for the global burden of disease study. Lancet Glob Health 2021; 9: e144-e160.

[3] Lotfy M, Adeghate J, Kalasz H, Singh J and Adeghate E. Chronic complications of diabetes mellitus: a mini review. Curr Diabetes Rev 2017; 13: 3-10.

[4] Chong DD, Das N and Singh RP. Diabetic retinopathy: screening, prevention, and treatment. Cleve Clin J Med 2024; 91: 503-510.

[5] Bressler NM, Beaulieu WT, Glassman AR, Blinder KJ, Bressler SB, Jampol LM, Melia M and Wells JA 3rd; Diabetic Retinopathy Clinical Research Network. Persistent macular thickening following intravitreous aflibercept, bevacizumab, or ranibizumab for central-involved diabetic macular edema with vision impairment: a secondary analysis of a randomized clinical trial. JAMA Ophthalmol 2018; 136: 257-269.
[6] Kim EJ, Lin WV, Rodriguez SM, Chen A, Loya A and Weng CY. Treatment of diabetic macular edema. Curr Diab Rep 2019; 19: 68.
[7] Zerhouni EA. Translational and clinical science–time for a new vision. N Engl J Med 2005; 353: 1621-1623.
[8] Woolf SH. The meaning of translational research and why it matters. JAMA 2008; 299: 211-213.
[9] Omary RA and Grist TM. The translational medicine of 2030: bedside to biosphere. AJR Am J Roentgenol 2024; 223: e2431562.
[10] Fort DG, Herr TM, Shaw PL, Gutzman KE and Starren JB. Mapping the evolving definitions of translational research. J Clin Transl Sci 2017; 1: 60-66.
[11] Wang W and Lo ACY. Diabetic retinopathy: pathophysiology and treatments. Int J Mol Sci 2018; 19: 1816.
[12] Antonetti DA, Silva PS and Stitt AW. Current understanding of the molecular and cellular pathology of diabetic retinopathy. Nat Rev Endocrinol 2021; 17: 195-206.
[13] Curtis TM, Gardiner TA and Stitt AW. Microvascular lesions of diabetic retinopathy: clues towards understanding pathogenesis? Eye (Lond) 2009; 23: 1496-1508.
[14] Barber AJ, Lieth E, Khin SA, Antonetti DA, Buchanan AG and Gardner TW. Neural apoptosis in the retina during experimental and human diabetes. Early onset and effect of insulin. J Clin Invest 1998; 102: 783-791.
[15] Simó R, Stitt AW and Gardner TW. Neurodegeneration in diabetic retinopathy: does it really matter? Diabetologia 2018; 61: 1902-1912.
[16] Coughlin BA, Feenstra DJ and Mohr S. Müller cells and diabetic retinopathy. Vision Res 2017; 139: 93-100.
[17] Lee EJ, Kim M, Park S, Shim JH, Cho HJ, Park JA, Park K, Lee D, Kim JH, Jeong H, Matsuzaki F, Kim SY, Kim J, Yang H, Lee JS and Kim JW. Restoration of retinal regenerative potential of Müller glia by disrupting intercellular Prox1 transfer. Nat Commun 2025; 16: 2928.
[18] Krady JK, Basu A, Allen CM, Xu Y, LaNoue KF, Gardner TW and Levison SW. Minocycline reduces proinflammatory cytokine expression, microglial activation, and caspase-3 activation in a rodent model of diabetic retinopathy. Diabetes 2005; 54: 1559-1565.
[19] Yang X, Huo F, Liu B, Liu J, Chen T, Li J, Zhu Z and Lv B. Crocin inhibits oxidative stress and pro-inflammatory response of microglial cells associated with diabetic retinopathy through the activation of PI3K/Akt signaling pathway. J Mol Neurosci 2017; 61: 581-589.
[20] Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. Diabetes 2005; 54: 1615-1625.
[21] Rao H, Jalali JA, Johnston TP and Koulen P. Emerging roles of dyslipidemia and hyperglycemia in diabetic retinopathy: molecular mechanisms and clinical perspectives. Front Endocrinol (Lausanne) 2021; 12: 620045.
[22] Liu DD, Zhang CY, Zhang JT, Gu LM, Xu GT and Zhang JF. Epigenetic modifications and metabolic memory in diabetic retinopathy: beyond the surface. Neural Regen Res 2023; 18: 1441-1449.
[23] Kowluru RA, Kowluru A, Mishra M and Kumar B. Oxidative stress and epigenetic modifications in the pathogenesis of diabetic retinopathy. Prog Retin Eye Res 2015; 48: 40-61.
[24] Nathan DM; DCCT/EDIC Research Group. The diabetes control and complications trial/epidemiology of diabetes interventions and complications study at 30 years: overview. Diabetes Care 2014; 37: 9-16.
[25] Cani PD. Human gut microbiome: hopes, threats and promises. Gut 2018; 67: 1716-1725.
[26] Iatcu CO, Steen A and Covasa M. Gut microbiota and complications of Type-2 diabetes. Nutrients 2021; 14: 166.
[27] Koh A, De Vadder F, Kovatcheva-Datchary P and Bäckhed F. From dietary fiber to host physiology: short-chain fatty acids as key bacterial metabolites. Cell 2016; 165: 1332-1345.
[28] Hiler D, Chen X, Hazen J, Kupriyanov S, Carroll PA, Qu C, Xu B, Johnson D, Griffiths L, Frase S, Rodriguez AR, Martin G, Zhang J, Jeon J, Fan Y, Finkelstein D, Eisenman RN, Baldwin K and Dyer MA. Quantification of retinogenesis in 3D cultures reveals epigenetic memory and higher efficiency in IPSCs derived from rod photoreceptors. Cell Stem Cell 2015; 17: 101-115.
[29] Zhong X, Gutierrez C, Xue T, Hampton C, Vergara MN, Cao LH, Peters A, Park TS, Zambidis ET, Meyer JS, Gamm DM, Yau KW and Canto-Soler MV. Generation of three-dimensional retinal tissue with functional photoreceptors from human iPSCs. Nat Commun 2014; 5: 4047.
[30] Polešovská L, Trmačová S, Celiker C, Hrubá E, Gambin FM, Chochola V, Matušková V, Beli E and Bárta T. Unveiling the cellular and molecular mechanisms of diabetic retinopathy with human retinal organoids. Cell Death Dis 2025; 16: 892.
[31] de Lemos L, Antas P, Ferreira IS, Santos IP, Felgueiras B, Gomes CM, Brito C, Seabra MC and

Tenreiro S. Modelling neurodegeneration and inflammation in early diabetic retinopathy using 3D human retinal organoids. In Vitro Model 2024; 3: 33-48.
[32] Edwards KL, Moore BM, Ganser TS, Susaimanickam PJ, Sovell K, Martin Y, Jager LD, Willes AM, Moyer TH, Bowar L, Phillips MJ, Stewart R, Chu LF and Gamm DM. Robust generation of photoreceptor-dominant retinal organoids from porcine induced pluripotent stem cells. Stem Cell Reports 2025; 20: 102425.
[33] Liu H, Ma Y, Gao N, Zhou Y, Li G, Zhu Q, Liu X, Li S, Deng C, Chen C, Yang Y, Ren Q, Hu H, Cai Y, Chen M, Xue Y, Zhang K, Qu J and Su J. Identification and characterization of human retinal stem cells capable of retinal regeneration. Sci Transl Med 2025; 17: eadp6864.
[34] Wu W, Ma G, Qi H, Dong L, Chen F, Wang Y, Mao X, Guo X, Cui J, Matsubara JA, Vanhaesebroeck B, Yan X, Zhao G, Zhang S and Lei H. Genome editing of Pik3cd impedes abnormal retinal angiogenesis. Hum Gene Ther 2023; 34: 30-41.
[35] Dueñas ME, Peltier-Heap RE, Leveridge M, Annan RS, Büttner FH and Trost M. Advances in high-throughput mass spectrometry in drug discovery. EMBO Mol Med 2023; 15: e14850.
[36] Wang R, Gao Y, Liu A and Zhai G. A review of nanocarrier-mediated drug delivery systems for posterior segment eye disease: challenges analysis and recent advances. J Drug Target 2021; 29: 687-702.
[37] Platania CBM, Pittalà V, Pascale A, Marchesi N, Anfuso CD, Lupo G, Cristaldi M, Olivieri M, Lazzara F, Di Paola L, Drago F and Bucolo C. Novel indole derivatives targeting HuR-mRNA complex to counteract high glucose damage in retinal endothelial cells. Biochem Pharmacol 2020; 175: 113908.
[38] Cai H, Gong J, Abriola L, Hoyer D, Noggle S, Paull D, Del Priore LV and Fields MA; Nyscf Global Stem Cell Array Team. High-throughput screening identifies compounds that protect RPE cells from physiological stressors present in AMD. Exp Eye Res 2019; 185: 107641.
[39] Yin Y, Wu S, Niu L and Huang S. High-throughput sequencing data reveal an antiangiogenic role of HNF4A-mediated CACNA1A/VEGFA axis in proliferative diabetic retinopathy. Invest Ophthalmol Vis Sci 2023; 64: 32.
[40] Brown DM, Nguyen QD, Marcus DM, Boyer DS, Patel S, Feiner L, Schlottmann PG, Rundle AC, Zhang J, Rubio RG, Adamis AP, Ehrlich JS and Hopkins JJ; RIDE and RISE Research Group. Long-term outcomes of ranibizumab therapy for diabetic macular edema: the 36-month results from two phase III trials: RISE and RIDE. Ophthalmology 2013; 120: 2013-2022.
[41] Writing Committee for the Diabetic Retinopathy Clinical Research Network, Gross JG, Glassman AR, Jampol LM, Inusah S, Aiello LP, Antoszyk AN, Baker CW, Berger BB, Bressler NM, Browning D, Elman MJ, Ferris FL 3rd, Friedman SM, Marcus DM, Melia M, Stockdale CR, Sun JK and Beck RW. Panretinal photocoagulation vs intravitreous ranibizumab for proliferative diabetic retinopathy: a randomized clinical trial. JAMA 2015; 314: 2137-2146.
[42] Zheng X, Wan J and Tan G. The mechanisms of NLRP3 inflammasome/pyroptosis activation and their role in diabetic retinopathy. Front Immunol 2023; 14: 1151185.
[43] Yang Y, Jiang G, Huang R, Liu Y, Chang X and Fu S. Targeting the NLRP3 inflammasome in diabetic retinopathy: from pathogenesis to therapeutic strategies. Biochem Pharmacol 2023; 212: 115569.
[44] Ritu, Goyal RK, Narwal S, Bhatt A, Sehrawat R, Devi P, Gulati M and Singla RK. Role of MMP-9 and NF-κB in diabetic retinopathy: progression and potential role of bioflavonoids in the mitigation of diabetic retinopathy. Curr Med Chem 2025; 32: 4992-5007.
[45] Hong L, Lin Y, Yang X, Wu T, Zhang Y, Xie Z, Yu J, Zhao H, Yi G and Fu M. A narrative review of STAT proteins in diabetic retinopathy: from mechanisms to therapeutic prospects. Ophthalmol Ther 2022; 11: 2005-2026.
[46] Yao Y, Du J, Li R, Zhao L, Luo N, Zhai JY and Long L. Association between ICAM-1 level and diabetic retinopathy: a review and meta-analysis. Postgrad Med J 2019; 95: 162-168.
[47] Xu M, Chen X, Yu Z and Li X. Receptors that bind to PEDF and their therapeutic roles in retinal diseases. Front Endocrinol (Lausanne) 2023; 14: 1116136.
[48] Sharma I, Yadav KS and Mugale MN. Redoxisome and diabetic retinopathy: pathophysiology and therapeutic interventions. Pharmacol Res 2022; 182: 106292.
[49] Simó R, Hernández C, Porta M, Bandello F, Grauslund J, Harding SP, Aldington SJ, Egan C, Frydkjaer-Olsen U, García-Arumí J, Gibson J, Lang GE, Lattanzio R, Massin P, Midena E, Ponsati B, Ribeiro L, Scanlon P, Lobo C, Costa MÂ and Cunha-Vaz J; European Consortium for the Early Treatment of Diabetic Retinopathy (EUROCONDOR). Effects of topically administered neuroprotective drugs in early stages of diabetic retinopathy: results of the EUROCONDOR clinical trial. Diabetes 2019; 68: 457-463.
[50] Parmar UM, Jalgaonkar MP, Kulkarni YA and Oza MJ. Autophagy-nutrient sensing pathways in diabetic complications. Pharmacol Res 2022; 184: 106408.
[51] Busik JV. Lipid metabolism dysregulation in diabetic retinopathy. J Lipid Res 2021; 62: 100017.

[52] Jiang F, Lei C, Chen Y, Zhou N and Zhang M. The complement system and diabetic retinopathy. Surv Ophthalmol 2024; 69: 575-584.
[53] Fu DJ, Bagga P, Naik G, Glinton S, Faes L, Liefers B, Lima R, Wignall G, Keane PA, Ioannidou E, Ribeiro Reis AP, McKeown A, Scheibler L, Patel PJ, Moghul I, Pontikos N and Balaskas K. Pegcetacoplan treatment and consensus features of geographic atrophy over 24 months. JAMA Ophthalmol 2024; 142: 548-558.
[54] Sha L, Zhao Y, Li S, Wei D, Tao Y and Wang Y. Insights to Ang/Tie signaling pathway: another rosy dawn for treating retinal and choroidal vascular diseases. J Transl Med 2024; 22: 898.
[55] Wykoff CC, Abreu F, Adamis AP, Basu K, Eichenbaum DA, Haskova Z, Lin H, Loewenstein A, Mohan S, Pearce IA, Sakamoto T, Schlottmann PG, Silverman D, Sun JK, Wells JA, Willis JR and Tadayoni R; YOSEMITE and RHINE Investigators. Efficacy, durability, and safety of intravitreal faricimab with extended dosing up to every 16 weeks in patients with diabetic macular oedema (YOSEMITE and RHINE): two randomised, double-masked, phase 3 trials. Lancet 2022; 399: 741-755.
[56] Wu Q, Liu C, Shu X and Duan L. Mechanistic and therapeutic perspectives of non-coding RNA-modulated apoptotic signaling in diabetic retinopathy. Cell Biol Toxicol 2024; 40: 53.
[57] Li EH, Huang QZ, Li GC, Xiang ZY and Zhang X. Effects of miRNA-200b on the development of diabetic retinopathy by targeting VEGFA gene. Biosci Rep 2017; 37: BSR20160572.
[58] Xue L, Xiong C, Li J, Ren Y, Zhang L, Jiao K, Chen C and Ding P. miR-200-3p suppresses cell proliferation and reduces apoptosis in diabetic retinopathy via blocking the TGF-β2/Smad pathway. Biosci Rep 2020; 40: BSR20201545.
[59] Assmann TS, Duarte GCK, Brondani LA, de Freitas PHO, Martins ÉM, Canani LH and Crispim D. Polymorphisms in genes encoding miR-155 and miR-146a are associated with protection to type 1 diabetes mellitus. Acta Diabetol 2017; 54: 433-441.
[60] Tiwari A, Mukherjee B and Dixit M. MicroRNA key to angiogenesis regulation: MiRNA biology and therapy. Curr Cancer Drug Targets 2018; 18: 266-277.
[61] Cataldi S, Tramontano M, Costa V, Aprile M and Ciccodicola A. Diabetic retinopathy: are lncRNAs new molecular players and targets? Antioxidants (Basel) 2022; 11: 2021.
[62] Yan B, Tao ZF, Li XM, Zhang H, Yao J and Jiang Q. Aberrant expression of long noncoding RNAs in early diabetic retinopathy. Invest Ophthalmol Vis Sci 2014; 55: 941-951.
[63] Liu JY, Yao J, Li XM, Song YC, Wang XQ, Li YJ, Yan B and Jiang Q. Pathogenic role of lncRNA-MALAT1 in endothelial cell dysfunction in diabetes mellitus. Cell Death Dis 2014; 5: e1506.
[64] Zhang YL, Hu HY, You ZP, Li BY and Shi K. Targeting long non-coding RNA MALAT1 alleviates retinal neurodegeneration in diabetic mice. Int J Ophthalmol 2020; 13: 213-219.
[65] Chen Z, Yang J, Gao Y, Jiang S, Li Z, Wang Y, Hu Z, Han F and Ni N. LncRNA MALAT1 aggravates the retinal angiogenesis via miR-320a/HIF-1α axis in diabetic retinopathy. Exp Eye Res 2022; 218: 108984.
[66] Sathishkumar C, Prabu P, Mohan V and Balasubramanyam M. Linking a role of lncRNAs (long non-coding RNAs) with insulin resistance, accelerated senescence, and inflammation in patients with type 2 diabetes. Hum Genomics 2018; 12: 41.
[67] Zhang J, Chen M, Chen J, Lin S, Cai D, Chen C and Chen Z. Long non-coding RNA MIAT acts as a biomarker in diabetic retinopathy by absorbing miR-29b and regulating cell apoptosis. Biosci Rep 2017; 37: BSR20170036.
[68] Zhou HR and Kuang HY. Circular RNAs: novel target of diabetic retinopathy. Rev Endocr Metab Disord 2021; 22: 205-216.
[69] Yao MD, Jiang Q, Ma Y, Zhu Y, Zhang QY, Shi ZH, Zhao C and Yan B. Targeting circular RNA-MET for anti-angiogenesis treatment via inhibiting endothelial tip cell specialization. Mol Ther 2022; 30: 1252-1264.
[70] Jiang Q, Liu C, Li CP, Xu SS, Yao MD, Ge HM, Sun YN, Li XM, Zhang SJ, Shan K, Liu BH, Yao J, Zhao C and Yan B. Circular RNA-ZNF532 regulates diabetes-induced retinal pericyte degeneration and vascular dysfunction. J Clin Invest 2020; 130: 3833-3847.
[71] Lu S and Cai J. Targeting therapy of PI3K/AKT signaling pathway via non-coding RNAs in diabetic retinopathy. Naunyn Schmiedebergs Arch Pharmacol 2025; 398: 11493-11504.
[72] He H, Zhang J, Gong W, Liu M, Liu H, Li X, Wu Y and Lu Q. Involvement of CircRNA expression profile in diabetic retinopathy and its potential diagnostic value. Front Genet 2022; 13: 833573.
[73] Zhang QY, Zhang HY, Feng SG, Yao MD, Ding JJ, Li XM, Ye R, Liu Q, Yao J and Yan B. Macrophage metabolic reprogramming ameliorates diabetes-induced microvascular dysfunction. Redox Biol 2025; 79: 103449.
[74] Su R, Zhou M, Lin J, Shan G and Huang C. A circular RNA-gawky-chromatin regulatory axis modulates stress-induced transcription. Nucleic Acids Res 2024; 52: 3702-3721.
[75] Gong X, Liu Y, Wu G, Xu Z, Zeng L, Tian M, Zhang R, Zeng C and Chen Y. An updated resource for the detection of protein-coding circRNA with CircProPlus. Sci Rep 2024; 14: 19040.

[76] Dugel PU, Koh A, Ogura Y, Jaffe GJ, Schmidt-Erfurth U, Brown DM, Gomes AV, Warburton J, Weichselberger A and Holz FG; HAWK and HARRIER Study Investigators. HAWK and HARRIER: phase 3, multicenter, randomized, double-masked trials of brolucizumab for neovascular age-related macular degeneration. Ophthalmology 2020; 127: 72-84.

[77] Cen S, Liu S, Zhao M and Tang L. Comparative efficacy and safety of faricimab, aflibercept, conbercept, and ranibizumab for neovascular age-related macular degeneration: a systematic review and network meta-analysis. Eur J Pharmacol 2026; 1010: 178406.

[78] Monés J, Srivastava SK, Jaffe GJ, Tadayoni R, Albini TA, Kaiser PK, Holz FG, Korobelnik JF, Kim IK, Pruente C, Murray TG and Heier JS. Risk of inflammation, retinal vasculitis, and retinal occlusion-related events with brolucizumab: post hoc review of HAWK and HARRIER. Ophthalmology 2021; 128: 1050-1059.

[79] Mesquida M, Molins B, Llorenç V, de la Maza MS and Adán A. Targeting interleukin-6 in autoimmune uveitis. Autoimmun Rev 2017; 16: 1079-1089.

[80] Yanagi Y, Ichikawa H, Nguyen LBT, Hayashi A, Abe N, Abe H and Uchida S. mRNA vaccination mitigates pathological retinochoroidal neovascularization in animal models. Vaccine 2025; 61: 127451.

[81] Supe S, Upadhya A, Tripathi S, Dighe V and Singh K. Liposome-polyethylenimine complexes for the effective delivery of HuR siRNA in the treatment of diabetic retinopathy. Drug Deliv Transl Res 2023; 13: 1675-1698.

[82] Hnik P, Boyer DS, Grillone LR, Clement JG, Henry SP and Green EA. Antisense oligonucleotide therapy in diabetic retinopathy. J Diabetes Sci Technol 2009; 3: 924-930.

[83] Hou X, Zaks T, Langer R and Dong Y. Lipid nanoparticles for mRNA delivery. Nat Rev Mater 2021; 6: 1078-1094.

[84] Springer AD and Dowdy SF. GalNAc-siRNA conjugates: leading the way for delivery of RNAi therapeutics. Nucleic Acid Ther 2018; 28: 109-118.

[85] Dalkara D, Byrne LC, Klimczak RR, Visel M, Yin L, Merigan WH, Flannery JG and Schaffer DV. In vivo-directed evolution of a new adeno-associated virus for therapeutic outer retinal gene delivery from the vitreous. Sci Transl Med 2013; 5: 189ra76.

[86] Grishanin R, Vuillemenot B, Sharma P, Keravala A, Greengard J, Gelfman C, Blumenkrantz M, Lawrence M, Hu W, Kiss S and Gasmi M. Preclinical evaluation of ADVM-022, a novel gene therapy approach to treating wet age-related macular degeneration. Mol Ther 2019; 27: 118-129.

[87] Zhong Y, Xia J, Liao L and Momeni MR. Non-coding RNAs and exosomal non-coding RNAs in diabetic retinopathy: a narrative review. Int J Biol Macromol 2024; 259: 128182.

[88] Garba AO and Mousa SA. Bevasiranib for the treatment of wet, age-related macular degeneration. Ophthalmol Eye Dis 2010; 2: 75-83.

[89] Kleinman ME, Yamada K, Takeda A, Chandrasekaran V, Nozaki M, Baffi JZ, Albuquerque RJ, Yamasaki S, Itaya M, Pan Y, Appukuttan B, Gibbs D, Yang Z, Karikó K, Ambati BK, Wilgus TA, DiPietro LA, Sakurai E, Zhang K, Smith JR, Taylor EW and Ambati J. Sequence- and target-independent angiogenesis suppression by siRNA via TLR3. Nature 2008; 452: 591-597.

[90] Nguyen QD, Schachar RA, Nduaka CI, Sperling M, Basile AS, Klamerus KJ, Chi-Burris K, Yan E, Paggiarino DA, Rosenblatt I, Aitchison R and Erlich SS; DEGAS Clinical Study Group. Dose-ranging evaluation of intravitreal siRNA PF-04523655 for diabetic macular edema (the DEGAS study). Invest Ophthalmol Vis Sci 2012; 53: 7666-7674.

[91] Nguyen QD, Schachar RA, Nduaka CI, Sperling M, Klamerus KJ, Chi-Burris K, Yan E, Paggiarino DA, Rosenblatt I, Aitchison R and Erlich SS; MONET Clinical Study Group. Evaluation of the siRNA PF-04523655 versus ranibizumab for the treatment of neovascular age-related macular degeneration (MONET Study). Ophthalmology 2012; 119: 1867-1873.

[92] Cunningham ET Jr, Adamis AP, Altaweel M, Aiello LP, Bressler NM, D'Amico DJ, Goldbaum M, Guyer DR, Katz B, Patel M and Schwartz SD; Macugen Diabetic Retinopathy Study Group. A phase II randomized double-masked trial of pegaptanib, an anti-vascular endothelial growth factor aptamer, for diabetic macular edema. Ophthalmology 2005; 112: 1747-1757.

[93] Liu J, Zhang F and Shi X. The role of metal nanocarriers, liposomes and chitosan-based nanoparticles in diabetic retinopathy treatment: a review study. Int J Biol Macromol 2025; 291: 139017.

[94] Liu Y and Wu N. Progress of nanotechnology in diabetic retinopathy treatment. Int J Nanomedicine 2021; 16: 1391-1403.

[95] Yang F, Zhang L, Li Z, Zhang M, Deng X, Sun D, Jiang M, Gui S, Du Y, Guo S, Zhou Q, Zhan Z, Gong H, Zhang Y, Zhou Y, Su Y and Lan Y. Hybrid cell-membrane-coated biomimetic nanoparticles for targeted noninvasive intervention in early diabetic retinopathy. Acta Biomater 2025: [Epub ahead of print].

[96] Iyer S, Lee C and Amiji MM. Biodegradable polymeric microsphere formulations of full-length anti-VEGF antibody bevacizumab for sustained intraocular delivery. Drug Deliv Transl Res 2025; 15: 3149-3160.

[97] Wen L, Gan M, Xiong S, Dai L, Chen W and Shi W. Thermosensitive hydrogel composite with si-Cx43 nanoparticles and anti-VEGF agent for synergistic treatment of diabetic retinopathy. Mater Today Bio 2025; 33: 101917.
[98] Chang W, Lv X, Zhu J, Shen JJ, Yao J, Liu Z and Chen Q. Multifunctional nanotherapeutics with long-acting release against macular degeneration by minimally invasive administration. ACS Nano 2024; 18: 19649-19662.
[99] Holekamp NM, Campochiaro PA, Chang MA, Miller D, Pieramici D, Adamis AP, Brittain C, Evans E, Kaufman D, Maass KF, Patel S, Ranade S, Singh N, Barteselli G and Regillo C; all Archway Investigators. Archway randomized phase 3 trial of the port delivery system with ranibizumab for neovascular age-related macular degeneration. Ophthalmology 2022; 129: 295-307.
[100] Cuello-Rodríguez S, Blanco-Fernández G, García-Otero X, Díaz-Tome V, Otero-Espinar FJ and Seoane-Viaño I. Long acting injectables & implants: advances in intraocular drug delivery. Int J Pharm 2025; 683: 126058.
[101] Ambati J and Adamis AP. Transscleral drug delivery to the retina and choroid. Prog Retin Eye Res 2002; 21: 145-151.
[102] Fitaihi R, Abukhamees S, Orlu M and Craig DQM. Transscleral delivery of dexamethasone-loaded microparticles using a dissolving microneedle array. Pharmaceutics 2023; 15: 1622.
[103] Tao Y, Li C, Yao A, Qu Y, Qin L, Xiong Z, Zhang J and Wang W. Intranasal administration of erythropoietin rescues the photoreceptors in degenerative retina: a noninvasive method to deliver drugs to the eye. Drug Deliv 2019; 26: 78-88.
[104] Noma H, Mimura T, Yasuda K, Motohashi R, Kotake O and Shimura M. Aqueous humor levels of soluble vascular endothelial growth factor receptor and inflammatory factors in diabetic macular edema. Ophthalmologica 2017; 238: 81-88.
[105] Gomułka K and Ruta M. The role of inflammation and therapeutic concepts in diabetic retinopathy-a short review. Int J Mol Sci 2023; 24: 1024.
[106] Gulshan V, Peng L, Coram M, Stumpe MC, Wu D, Narayanaswamy A, Venugopalan S, Widner K, Madams T, Cuadros J, Kim R, Raman R, Nelson PC, Mega JL and Webster DR. Development and validation of a deep learning algorithm for detection of diabetic retinopathy in retinal fundus photographs. JAMA 2016; 316: 2402-2410.
[107] Abràmoff MD, Lavin PT, Birch M, Shah N and Folk JC. Pivotal trial of an autonomous AI-based diagnostic system for detection of diabetic retinopathy in primary care offices. NPJ Digit Med 2018; 1: 39.
[108] Nadeem MW, Goh HG, Hussain M, Liew SY, Andonovic I and Khan MA. Deep learning for diabetic retinopathy analysis: a review, research challenges, and future directions. Sensors (Basel) 2022; 22: 6780.
[109] Khan Z, Kuriakose RK, Khan M, Chin EK and Almeida DR. Efficacy of the intravitreal sustained-release dexamethasone implant for diabetic macular edema refractory to anti-vascular endothelial growth factor therapy: meta-analysis and clinical implications. Ophthalmic Surg Lasers Imaging Retina 2017; 48: 160-166.
[110] Alsoudi AF, Wai KM, Koo E, Parikh R, Mruthyunjaya P and Rahimy E. Initial therapy of panretinal photocoagulation vs anti-VEGF injection for proliferative diabetic retinopathy. JAMA Ophthalmol 2024; 142: 972-975.
[111] Wat N, Wong RL and Wong IY. Associations between diabetic retinopathy and systemic risk factors. Hong Kong Med J 2016; 22: 589-599.
[112] Boyer DS, Yoon YH, Belfort R Jr, Bandello F, Maturi RK, Augustin AJ, Li XY, Cui H, Hashad Y and Whitcup SM; Ozurdex MEAD Study Group. Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. Ophthalmology 2014; 121: 1904-1914.
[113] Campochiaro PA, Brown DM, Pearson A, Chen S, Boyer D, Ruiz-Moreno J, Garretson B, Gupta A, Hariprasad SM, Bailey C, Reichel E, Soubrane G, Kapik B, Billman K, Kane FE and Green K; FAME Study Group. Sustained delivery fluocinolone acetonide vitreous inserts provide benefit for at least 3 years in patients with diabetic macular edema. Ophthalmology 2012; 119: 2125-2132.
[114] Salvetat ML, Pellegrini F, Spadea L, Salati C, Musa M, Gagliano C and Zeppieri M. The treatment of diabetic retinal edema with intravitreal steroids: How and When. J Clin Med 2024; 13: 1327.
[115] Lv YX, Li QY, Duan P, Zhang MF, Liu B, Li SY, Zhao TT, Wang H, Liu Y and Yin ZQ. Safe CNV removal is crucial for successful hESC-RPE transplantation in wet age-related macular degeneration. Stem Cell Reports 2025; 20: 102424.
[116] Holz FG, Le Mer Y, Muqit MMK, Hattenbach LO, Cusumano A, Grisanti S, Kodjikian L, Pileri MA, Matonti F, Souied E, Stanzel BV, Szurman P, Weber M, Bartz-Schmidt KU, Eter N, Delyfer MN, Girmens JF, van Overdam KA, Wolf A, Hornig R, Corazzol M, Brodie F, Olmos de Koo L, Palanker D and Sahel JA. Subretinal photovoltaic implant to restore vision in geographic atrophy due to AMD. N Engl J Med 2026; 394: 232-242.