Emerging solutions for neovascular age-related macular degeneration

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Purpose of review
To summarize emerging therapeutic strategies for neovascular (wet) age-related macular degeneration (nAMD), with emphasis on recent translational and clinical developments.

Recent findings
The nAMD treatment landscape is rapidly evolving. Gene therapies (e.g. ABBV-RGX-314, ADVM-022, and 4D-150) have demonstrated sustained intraocular anti-VEGF expression with reduced injection burden in phase 2 and 3 programs, validating the 'biofactory' concept. Tyrosine kinase inhibitors delivered via intravitreal or suprachoroidal implants (e.g. EYP-1901, OTX-TKI, and CLS-AX) show potential for twice-yearly or less frequent dosing. Moreover, emerging therapeutic approaches increasingly target non-VEGF pathogenic pathways, reflecting a shift toward mechanistically diverse vascular stabilization and neuroprotection strategies. These include multitargeted biologics that couple anti-angiogenic and anti-inflammatory effects (e.g. KSI-501, IBI-302, and AG-73305), as well as agents modulating FGF2 signaling, Wnt activation, complement regulation, and cellular metabolism.

Summary
Therapeutic innovation in nAMD is transitioning from incremental refinements in intravitreal anti-VEGF delivery to strategies aimed at extending durability or targeting alternative contributory pathways. Long-term safety, efficacy, and durability will determine which of these candidates redefine standard care.

Keywords
bispecific biologics, emerging therapeutics, gene therapy, neovascular age-related macular degeneration, tyrosine kinase inhibitors

INTRODUCTION

Age-related macular degeneration (AMD) remains a leading cause of vision loss among older adults [1,2], with neovascular (wet) AMD (nAMD) historically responsible for most cases of severe vision loss and legal blindness from the disease [3,4]. Although intravitreal anti-vascular endothelial growth factor (VEGF) therapy has revolutionized treatment, challenges remain. Chief among these are high treatment burden, lack of curative potential, and risk of nonadherence, suboptimal response, or tachyphylaxis [5–7]. This, in turn, has spurred interest in new therapeutic strategies to extend durability, facilitate delivery, and target alternative contributory pathways. Notably, faricimab – the first bispecific therapy for nAMD, targeting both VEGF-A and angiopoietin-2 (Ang-2) – was approved in 2022 [8], demonstrating the feasibility of multipathway inhibition and, more broadly, the value of developing innovative nAMD strategies that extend beyond current treatment paradigms. At present, there exists a rich pipeline of emerging therapies for nAMD including gene therapies, tyrosine kinase inhibitors (TKIs), multitargeted biologics, novel delivery platforms, and repurposed systemic drugs. This review summarizes key emerging treatments for nAMD, emphasizing those with active US clinical trials and regulatory activity through mid-2025 (Table 1). We also review recent developments in basic and translational research, which have served to identify novel therapeutic targets for nAMD.

GENE THERAPY

A highly anticipated therapeutic strategy in nAMD is gene therapy, which involves use of viral vectors

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KEY POINTS

- Emerging therapies for neovascular (wet) age-related macular degeneration (nAMD) are expanding beyond injection-administered anti-VEGF monotherapy toward longer acting and multipathway approaches.
- Gene therapy offers the potential for substantially reduced treatment burden through sustained intraocular anti-VEGF expression, with long-term durability and safety still to be determined.
- Tyrosine kinase inhibitors delivered via intravitreal and suprachoroidal routes have demonstrated meaningful reductions in injection frequency, while other formulations continue to face challenges.
- Multitarget biologics that couple anti-angiogenic and anti-inflammatory mechanisms show biologic appeal, with clinical superiority over standard anti-VEGF therapy still to be consistently demonstrated.
- Novel strategies targeting Wnt signaling, fibroblast growth factor 2 (FGF2), complement activation, immunometabolism, and photoreceptor metabolism reflect a broader reconceptualization of nAMD as a multifactorial vascular-inflammatory-metabolic disease.

to deliver genetic payloads that enable the patient's own retinal cells to produce anti-angiogenic factors *in situ*. This 'biofactory' concept could potentially reduce or eliminate the need for anti-VEGF injections, with several candidate therapies recently reaching phase 2 or 3 trials. ABBV-RGX-314 (surabgene lomparvovec) [AbbVie, North Chicago (Illinois), U.S. and Regenxbio, Rockville (Maryland), U.S.] is an adeno-associated virus serotype 8 (AAV8)-vectored gene therapy encoding a ranibizumab-like anti-VEGF Fab, currently being evaluated via both subretinal and suprachoroidal delivery [9,10▪▪,11]. In a phase 2 study of subretinally delivered ABBV-RGX-314 in previously-treated nAMD eyes (NCT04832724), 60–73% of patients remained injection-free at 6 months, with stable or improved visual acuity and retinal thickness across all dosing cohorts [9]. In a fellow-eye sub-study (NCT03999801), treated second eyes experienced a 93% reduction in treatment burden at 12 months, with 60% remaining injection-free [11]. The pivotal Phase 2b/3 ATMOSPHERE (NCT04704921; ranibizumab comparator) and Phase 3 ASCENT (NCT05407636; aflibercept comparator) trials recently completed enrollment, with planned primary endpoints of non-inferiority in change in visual acuity [12]. In parallel, the Phase 2 AAVIATE trial (NCT04514653) is currently evaluating suprachoroidal delivery of ABBV-RGX-314, with interim 6-month results demonstrating a 68–80% reduction in anti-VEGF injection rate [13].

Ixoberogene soroparvovec (ixo-vec, ADVM-022) [Adverum Biotechnologies, Redwood City (California), U.S.] uses an intravitreal injection to deliver an AAV2.7m8 vector carrying an aflibercept-encoding payload [14,15]. Notably, AAV2.7m8 was designed from AAV2 to enhance retinal transduction after intravitreal administration, although it remains susceptible to inflammation and to preexisting anti-AAV2 immunity [16,17]. In view of inflammation-related complications in earlier studies [18▪,19], the Phase 2 LUNA trial (NCT05536973) assessed ixo-vec in combination with four prophylaxis regimens (i.e. topical corticosteroids with or without intravitreal corticosteroid implant, with or without oral corticosteroids). Associated 52-week data were positive: 54–69% of treated eyes required no rescue injection, with an 88–92% reduction in anti-VEGF injection rate. Importantly, no significant intraocular inflammation was observed across all participants [14,15]. The Phase 3 ARTEMIS trial (NCT06856577) is underway to assess non-inferiority versus aflibercept.

Another intravitreally delivered AAV gene therapy, 4D-150 [4D Molecular Therapeutics, Emeryville (California), U.S.], uses a proprietary AAV-R100 capsid engineered to achieve improved intravitreal retinal gene transfer compared to AAV2 [20▪▪]. The construct delivers two transgenes: one expressing aflibercept and another expressing a micro-RNA (miRNA)-suppressing VEGF-C [20▪▪,21]. In the ongoing Phase 1/2 PRISM trial (NCT05197270), 4D-150 demonstrated an 83% reduction in injection burden at 52 weeks versus every 8 week (q8w) aflibercept, with 57% of patients remaining injection-free [21]. The pivotal phase 3 trials, 4FRONT-1 (NCT06864988) and 4FRONT-2 (NCT07064759), are currently enrolling.

Expanding interest in gene therapy is further exemplified by several candidates at earlier stages of development. These include EXG102–031 [Exegenesis Bio, Horsham (Pennsylvania), U.S.], which employs a subretinally delivered AAV vector encoding a soluble faricimab-like VEGF/Ang-2 trap [22], and is currently undergoing phase 1 evaluation (Everest NCT05903794). ABI-110 [Avirmax Therapeutics, Hayward (California), U.S.] and SKG0106 [Skyline Therapeutics, Shanghai, China] are intravitreal AAV gene therapies encoding VEGF traps [23,24], both in phase 1/2 testing (NCT06550011 and NCT05986864). Together, these gene therapies – though differing in vector, payload, and route of administration – offer the shared promise of reduced treatment burden in nAMD if successful. Nevertheless, long-term safety, efficacy, and durability remain to be demonstrated.

Table 1. Therapies for neovascular age-related macular degeneration currently in active or advancing clinical trials

Name (alternative names)	Company	Mechanism	Target	Delivery method	Active trials
Gene therapy					
ABBV-RGX-314 (surabgene lomparvovec)	AbbVie/ Regenxbio	AAV8-vectored gene therapy encoding anti-VEGF Fab (ranibizumab-like)	VEGF-A	Subretinal/ suprachoroidal	NCT04704921 (Phase 2b/3 ATMOSPHERE) NCT05407636 (Phase 3 ASCENT) NCT04514653 (Phase 2 AAVIATE)
Ixo-vec (ADVM-022; ixoberogene soroparvovec)	Adverum Biotechnologies	AAV2.7m8-vectored gene therapy encoding VEGF trap (aflibercept)	VEGF-A, VEGF-B, PlGF	Intravitreal	NCT05536973 (Phase 2 LUNA) NCT06856577 (Phase 3 ARTEMIS)
4D-150	4D Molecular Therapeutics	AAV-R100-vectored gene therapy encoding aflibercept and miRNA silencing VEGF-C	VEGF-A, VEGF-B and PlGF (via aflibercept) + VEGF-C (via miRNA silencing)	Intravitreal	NCT05197270 (Phase 1/2 PRISM) NCT06864988 (Phase 3 4FRONT-1) NCT07064759 (Phase 3 4FRONT-2)
EXG102-031	Exegenesis Bio	AAV-vectored gene therapy encoding bispecific VEGF/Ang-2 trap (faricimab-like)	VEGF-A + Ang-2	Subretinal	NCT05903794 (Phase 1 Everest)
ABI-110	Avirmax Therapeutics	AAV-vectored gene therapy encoding anti-VEGF fusion protein	VEGF-A (likely)	Intravitreal	NCT06550011 (Phase 1/2a)
SKG0106	Skyline Therapeutics	AAV-vectored gene therapy encoding VEGF trap	VEGF-A (likely)	Intravitreal	NCT05986864 (Phase 1/2)
Tyrosine Kinase Inhibitors					
OTX-TKI (axpaxli; axitinib implant)	Ocular Therapeutix	Bioresorbable hydrogel implant releasing axitinib	VEGFR-1,-2,-3, PDGFR	Intravitreal	NCT06223958 (Phase 3 SOL-1) NCT06495918 (Phase 3 SOL-R)
CLS-AX (axitinib injectable suspension)	Clearside Biomedical	Suspended axitinib injection for compartmental delivery	VEGFR-1,-2,-3, PDGFR	Suprachoroidal	NCT05891548 (Phase 2b ODYSSEY) - completed Phase 3 planned
AR-14034 (axitinib sustained-release implant)	Alcon Research	Bioerodible axitinib sustained-release implant	VEGFR-1,-2,-3, PDGFR	Intravitreal	NCT05769153 (Phase 1/2 NOVA-1)

Table 1 (*Continued*)

Name (alternative names)	Company	Mechanism	Target	Delivery method	Active trials
EYP-1901 (duravyu; vorolanib intravitreal insert)	EyePoint Pharmaceuticals	Bioerodible vorolanib sustained-release implant	VEGFR-1,-2,-3, PDGFR, FGFR	Intravitreal	NCT06683742 (Phase 3 LUCIA) NCT06668064 (Phase 3 LUGANO)
KHK4951 (topical tivozanib)	Kyowa Kirin	Nanocrystalline formulation of tivozanib	VEGFR-1,-2,-3	Topical (ophthalmic)	NCT06116890 (Phase 2)
D-4517.2 (migaldendranib)	Ashvattha Therapeutics	Hydroxyl-dendrimer–conjugated form of sunitinib	VEGFR-1,-2,-3, PDGFR (cell-targeted delivery)	Subcutaneous	NCT05387837 (Phase 2 TEJAS)
Multitarget and bispecific agents					
KSI-501	Kodiak Sciences	Bispecific antibody-biopolymer conjugate inhibiting VEGF-A and IL-6	VEGF-A + IL-6	Intravitreal	NCT06556368 (Phase 3 DAYBREAK)
RC28-E	RemeGen	Dual-target fusion protein combining VEGF and FGF2-binding domains	VEGF-A + FGF2	Intravitreal	NCT05727397 (Phase 3)
IBI-302 (efdamrofusp alfa)	Innovent Biologics	Recombinant fusion protein combining VEGFR-Fc decoy fused with complement binding fragment	VEGF-A, VEGF-B, PlGF (via VEGFR-Fc decoy) + C3b, C4b	Intravitreal	NCT05972473 (Phase 3 STAR)
Novel mechanistic targets					
MK-3000 (EYE-103; Restoret)	EyeBio/Merck	Wnt pathway-activating agonist antibody	FZD4, LRP5	Intravitreal	NCT06571045 (Phase 2b/3 BRUNELLO)
AXT107 (gersizangitide)	AsclepiX Therapeutics	Gel depot containing collagen IV–derived integrin-binding peptide that activates Tie2 and destabilizes VEGF/VEGFR2 interaction	Tie2, VEGF/VEGFR2 pathway modulation	Suprachoroidal	NCT05859776 (Phase 1/2a DISCOVER)
RBM-007	Ribomic	FGF2-specific RNA aptamer	FGF2	Intravitreal	NCT04200248 (Phase 2 TOFU) - complete NCT04640272 (Phase 2 RAMEN) - complete NCT04895293 (Phase 2 TEMPURA) - complete

TYROSINE KINASE INHIBITORS

Receptor tyrosine kinases (RTKs), including VEGF receptor (VEGFR)-1, VEGFR-2, VEGFR-3 and platelet-derived growth factor receptor (PDGFR), mediate angiogenesis and vessel stabilization [25–27]. As such, TKIs present a logical anti-angiogenic strategy. Relative to antibodies, TKIs are simpler and smaller molecules, thus presenting expanded opportunities for deployment in novel ophthalmic formulations or administration via non-ophthalmic routes (e.g. subcutaneous) [28,29]. OTX-TKI (axpaxli) [Ocular Therapeutix, Bedford (Massachusetts), U.S.] is a bioresorbable intravitreal hydrogel implant containing axitinib, a potent pan-VEGFR/PDGFR inhibitor [30]. Two phase 1 studies (NCT03630315 and NCT04989699) assessed OTX-TKI in previously treated eyes. In one of these studies, a single OTX-TKI implant maintained stable vision and retinal anatomy with a reduction in treatment burden of 89% at 12 months [30]. Two registrational phase 3 trials in treatment-naive disease – SOL-1 (NCT06223958) and SOL-R (NCT06495918) – are underway and assess superiority and non-inferiority versus aflibercept, respectively. Mechanistically related is CLS-AX [Clearside Biomedical, Alpharetta (Georgia), U.S.], which delivers axitinib into the suprachoroidal space [31,32,33▪]. In the Phase 2b ODYSSEY trial (NCT05891548) for previously treated nAMD patients, CLS-AX resulted in an 84% reduction in injection frequency at 6 months, with 67% of patients remaining injection-free [31,32]. A phase 3 program is planned per the company [34]. An additional axitinib-based therapy, AR-14034 [Alcon Research, Geneva, Switzerland], uses a bioerodible sustained-release intravitreal implant for delivery and is in phase 1/2 testing (NOVA-1, NCT05769153) [35].

Another TKI-based therapeutic, EYP-1901 (Duravyu) [EyePoint Pharmaceuticals, Watertown (Massachusetts), U.S.], delivers vorolanib – an inhibitor targeting VEGFR-1, VEGFR-2, VEGFR-3, PDGFR, and fibroblast growth factor receptor (FGFR) – via a bioerodible polymer implant [36▪]. In the Phase 2 DAVIO-2 trial (NCT05381948), a single EYP-1901 implant achieved noninferior visual acuity with stable anatomic outcomes at 12 months compared to q8w aflibercept, with 47–52% of eyes remaining injection free and an 81–83% reduction in anti-VEGF burden [37]. The pivotal Phase 3 LUCIA (NCT06683742) and LUGANO (NCT06668064) trials in previously treated and treatment-naive nAMD have completed recruitment. If approved, these TKI-based therapies could permit twice-yearly (or less frequent) dosing, substantially easing treatment burden for patients.

Alternative routes for TKI delivery are also being explored and offer a potential path to further reducing ophthalmic injection-related burden, but agents formulated for these routes have encountered significant challenges [29,38–42]. Nevertheless, still active in the pipeline is KHK4951 [Kyowa Kirin, Tokyo, Japan], a topical nanocrystalline formulation of tivozanib (a pan-VEGFR TKI) currently in phase 2 (NCT06116890) development. Also in early clinical testing is migaldendranib (D-4517.2) [Ashvattha Therapeutics, Redwood City (California), U.S.], a hydroxyl-dendrimer–conjugated form of sunitinib that selectively targets activated macrophages, microglia, and hypoxic RPE cells [43]. In the ongoing Phase 2 TEJAS trial (NCT05387837), subcutaneous migaldendranib every 2–4 weeks reduced anti-VEGF injection burden by 83% in study eyes and 89% in fellow eyes at 40 weeks [44,45].

MULTITARGET AND BISPECIFIC AGENTS

Given the multifactorial nature of nAMD and demonstrated clinical success of faricimab, there exists strong interest in simultaneously targeting multiple angiogenic or inflammatory pathways. This may not only improve efficacy but also enhance durability by addressing pathways involved in resistance or tachyphylaxis. Several bispecific or multitargeted molecules are in late-stage trials. KSI-501 [Kodiak Sciences, Palo Alto (California), U.S.] is a bispecific antibody–biopolymer conjugate that inhibits both VEGF-A and interleukin-6 (IL-6) [46,47]. IL-6 is a pro-inflammatory cytokine implicated in ocular exudation and fibrosis [48–53]. In preclinical models, KSI-501 normalized retinal vascular permeability more effectively than anti-VEGF alone [46]. The Phase 3 DAYBREAK trial (NCT06556368) for treatment-naive nAMD is ongoing and compares KSI-501 and KSI-301 (a mono-specific counterpart of KSI-501, targeting VEGF-A only) [54] to aflibercept control. RC28-E [RemeGen, Yantai, China], another dual-target biologic, combines a VEGF-binding domain with one binding fibroblast growth factor 2 (FGF2) [55▪]. Inhibition of FGF2 is conceptually attractive given its role in promoting angiogenesis and anti-VEGF resistance, especially in chronic lesions [56–58]. A phase 1b trial showed improvements in visual acuity (up to +10 ETDRS letters) and retinal thickness (up to −175 μm) at 48 weeks [55▪]. A phase 3 trial (NCT05727397) is recruiting.

IBI-302 (efdamrofusp alfa) [Innovent Biologics, Suzhou, China] is a bispecific decoy fusion protein comprised of two VEGF-binding domains fused with a complement receptor fragment targeting C3b/C4b, thereby suppressing both angiogenesis and complement-mediated inflammation [59▪▪]. In a phase 2 study (NCT05403749), IBI-302 demonstrated noninferior visual outcomes versus aflibercept through 52 weeks, with greater than 80% of patients maintained on at least 12-week dosing intervals. Intriguingly, macular atrophy incidence was lower with IBI-

302 versus aflibercept (4.7–5.1 versus 7.7%) [59▪▪]. A phase 3 trial (STAR NCT05972473) is currently underway. If successful, IBI-302 would introduce complement suppression as an adjunct strategy in nAMD despite evidence that complement inhibition may increase conversion to nAMD in geographic atrophy [60,61]. Together, multitarget agents hold biologic appeal and may improve durability, but prior attempts at pathway expansion have not consistently delivered superior clinical outcomes [62–64], underscoring the need for rigorous phase 3 validation.

NOVEL MECHANISTIC TARGETS

As exemplified by some of the aforementioned solutions, pathologic pathways outside of VEGF signaling are increasingly being targeted by emerging therapies, including several implicated in vascular stability. For instance, upregulation of Wnt/β-catenin signaling reduces leakage and promotes vascular quiescence by reinforcing the blood–retina barrier phenotype of endothelial cells [65–67]. MK-3000 (EYE-103, Restoret) [Merck, Rahway (New Jersey), U.S. and EyeBio, London, United Kingdom] is a Wnt-pathway agonist antibody that activates the frizzled-4 (FZD4) and low-density lipoprotein receptor-related protein 5 (LRP5) receptors, thereby upregulating downstream β-catenin signaling in endothelial cells [68]. In the Phase 1b/2a AMARONE study (NCT05919693), monthly intravitreal MK-3000 in combination with aflibercept gained ~7 ETDRS letters at 3 months with reduction in retinal thickness by greater than 200 μm within 1 month [68]. A phase 2b/3 trial of MK-3000 in diabetic macular edema (DME) is currently underway (BRUNELLO NCT06571045), though a phase 3 trial in nAMD has yet to be announced.

Another pathway involved in vascular stability is FGF2 signaling (as previously discussed in the context of RC28-E); though results from phase 2 studies (TOFU NCT04200248, RAMEN NCT04640272, and TEMPURA NCT04895293) for the FGF2-specific RNA aptamer RBM-007 [Ribomic, Tokyo, Japan] were mixed, the findings suggest possible utility in eyes with minimal or no anti-VEGF treatment history [69▪]. Similar to faricimab, AXT107 (gersizangitide) [AsclepiX Therapeutics, Baltimore (Maryland), U.S.] modulates the Tie2/Ang pathway to promote vascular stability [70]. Delivered as a suprachoroidal gel depot, AXT107 is a collagen IV-derived peptide that binds integrins in a manner that simultaneously causes Tie2 activation and destabilizes VEGF/VEGFR-2 interaction [70]. The Phase 1/2a DISCOVER trial (NCT05859776) completed enrollment in mid-2024, though efficacy data have yet to be released. AG-73305 [Allgenesis, Taipei, Taiwan] is a 'disintegrin fusion protein' combining a VEGF-trap moiety with an integrin-binding peptide, extending design principles from oncologic integrin inhibitors (e.g. cilengitide) [71]. Integrins on endothelial cells and RPE-mediate neovascular growth and vascular stability; inhibiting integrins can induce vessel regression and enhance anti-VEGF effects [72]. A phase 2a trial (NCT05301751) of AG-73305 in DME was recently completed with encouraging signals of extended durability and efficacy in a small patient cohort [71].

At the intersection of angiogenesis and inflammatory signaling are transcription factors (TFs), such as runt-related TF 1 (RUNX1) and reduction-oxidation factor 1 (Ref-1), which promote endothelial cell proliferation and choroidal neovascularization. Experimental inhibitors of Ref-1 are being tested in ocular neovascular models [73–79]. This work provides a biologic link between vascular instability and immune activation. Building on this concept, other emerging nAMD treatments target chronic inflammation and immune dysregulation. AKST4290 [Alkahest, Inc., San Carlos (California), U.S.] is an oral inhibitor of C-C chemokine receptor type 3 (CCR3) – a protein implicated in immune cell trafficking and choroidal neovascularization in preclinical models [80,81]. In a small phase 2a study (NCT00355806), treatment-naive patients receiving AKST4290 achieved a mean +7 ETDRS letter gain over 6 weeks [82]. The subsequent randomized Phase 2 PHTHALO-205 trial (NCT04331730) evaluated oral AKST4290 in combination with aflibercept for 36 weeks, but failed to demonstrate an additive visual benefit over aflibercept alone. Despite this lack of positive results, the early success of IL-6 targeting agents combined with emerging basic and translational research indicates targeting inflammation is still an area of promise [83,84]. For instance, researchers are exploring modulation of immunometabolism through inhibition of the enzyme phosphofructokinase-2/fructose-2,6-bisphosphatase 3 (PFKFB3) to downregulate glycolysis in activated macrophages. This, in turn, may reduce the angiogenic and inflammatory phenotype of these cells [85–87]. Though still preclinical, compounds targeting immunometabolic checkpoints represent interesting targets for future therapies.

Relatedly, strategies targeting metabolic pathways in other cell types, including endothelial and photoreceptor cells, hold similar promise. Pro-angiogenic growth factors rely on downstream metabolic adaptations in endothelial cells to induce proliferation, migration, and sprouting [88]. Thus, targeting these downstream metabolic adaptations has the potential to prevent angiogenesis despite concurrent pro-angiogenic signaling. For instance, dampening

of glycolysis in endothelial cells via inhibition of the aforementioned PFKFB3 has demonstrated anti-angiogenic benefits [89]. Additionally, small molecule inhibitors of ferrochelatase (FECH) modulating glycolysis and oxidative phosphorylation have been shown to downregulate known activators of angiogenesis in endothelial cells in preclinical models [90]. Interestingly, recent studies highlight the pivotal role of photoreceptor metabolism and degeneration in the initiation and progression of nAMD [91]. Clinical studies show that photoreceptor degeneration predicts conversion to neovascular disease, and preclinical studies demonstrate photoreceptor-specific metabolic dysfunction mediates pro-angiogenic inflammatory signals and drives pathologic neovascularization in the retina [92–95]. Yet, despite growing recognition that photoreceptor metabolic dysfunction and degeneration are more than just bystanders in disease progression, therapeutic strategies targeting photoreceptor metabolic adaptations are lacking. Addressing this critical gap is expected to reveal novel targets for therapeutic gain in nAMD.

REPURPOSED SYSTEMIC DRUGS

Beyond novel biologics and gene therapy, there is expanded interest in repurposing systemic agents that exert antiangiogenic, antioxidative, or anti-inflammatory effects. These agents, though developed for other diseases, engage molecular pathways that overlap with those implicated in nAMD pathogenesis. For instance, a protective effect has been proposed for metformin [96], which activates AMP-activated protein kinase (AMPK) to dampen inflammatory cytokine production and inhibit neovascularization [97–99]. However, existing work assessing metformin for AMD has shown mixed results and is largely observational, limiting causal inference [99,100▪▪,101]. As such, current evidence does not support prescribing metformin to prevent or slow AMD progression. Interestingly, metformin's putative ocular effects may extend beyond direct AMPK signaling; preclinical data suggests metformin can reduce choroidal neovascularization through modulation of the gut–retina axis [102]. This emerging line of research highlights a broader concept: the gut microbiome may influence retinal disease activity. Dietary interventions or probiotic treatments could eventually serve as adjuvants to reduce disease activity – a prediction based on existing science linking gut microbiome dysbiosis and diet (e.g. high-glycemic or high-fat diets) with chronic inflammation in nAMD [103–106].

Other exploratory agents include L-DOPA (which stimulates pigment epithelium-derived factor [PEDF] release via G-protein coupled receptor 143 [GPR143]) [107,108▪▪], doxycycline (which inhibits matrix metalloproteinase-2/9 [MMP-2/9], stabilizes Bruch's membrane, and inhibits macrophage M2 polarization) [109,110], systemic β-blockers (which reduce VEGF and IL-6 expression and modulate choroidal perfusion) [111–113,114▪], and statins (which suppress VEGF expression and attenuate oxidative stress in RPE and endothelial cells) [115–118]. These agents underscore how systemic metabolic, oxidative, and inflammatory modulation could complement current intraocular strategies to reduce treatment burden.

CONCLUSION

The therapeutic frontier in nAMD is broadening beyond injection-administered VEGF-A inhibition and toward sustained, multipathway modulation. Gene therapies may soon establish a new baseline of durability, while small-molecule and bispecific agents test the limits of non-antibody delivery and multitarget inhibition, respectively. Success will hinge on balancing potency, inflammation control, and predictable expression. Importantly, translational efforts now encompass pathways linked to angiogenesis resistance, complement activation, metabolic dysregulation, and cellular inflammation, reflecting a systemic view of retinal vascular disease. If current trajectories hold, the next decade will likely see a hybrid model: long-acting, locally expressed anti-VEGF platforms augmented by agents that address inflammation and vascular instability. Continued emphasis on safety, real-world durability, and equitable access will determine whether these innovations improve long-term visual outcomes while reducing treatment burden.

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