UNIVERSITY OF BIRMINGHAM

Emerging therapies and their delivery for treating age-related macular degeneration

Thomas, Chloe N; Sim, Dawn A; Lee, Wen Hwa; Alfahad, Nada; Dick, Andrew D; Denniston, Alastair; Hill, Lisa J

[Link to publication on Research at Birmingham portal](#)

REVIEW ARTICLE

Emerging therapies and their delivery for treating age-related macular degeneration

Chloe N. Thomas[1] | Dawn A. Sim[2,3] | Wen Hwa Lee[4,5] | Nada Alfahad[1] |
Andrew D. Dick[3,6] | Alastair K. Denniston[3,7,8,9,10,11] | Lisa J. Hill[1]

[1]School of Biomedical Sciences, Institute of Clinical Sciences, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK

[2]Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology, London, UK

[3]National Institute for Health Research (NIHR) Biomedical Research Centre at Moorfields Eye Hospital and University College London Institute of Ophthalmology, London, UK

[4]Action Against AMD, London, UK

[5]Affordable Medicines Programme, Oxford Martin School, University of Oxford, Oxford, UK

[6]Academic Unit of Ophthalmology, Bristol Medical School and School of Cellular and Molecular Medicine, University of Bristol, Bristol, UK

[7]Academic Unit of Ophthalmology, Institute of Inflammation and Ageing, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK

[8]Department of Ophthalmology, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

[9]Centre for Patient Reported Outcome Research, Institute of Applied Health Research, University of Birmingham, Birmingham, UK

[10]Birmingham Health Partners Centre for Regulatory Science and Innovation, University of Birmingham, Birmingham, UK

[11]Health Data Research UK, London, UK

Correspondence
Lisa J. Hill and Chloe N. Thomas, School of Biomedical Sciences, Institute of Clinical Sciences, College of Medical and Dental Sciences, University of Birmingham, Birmingham, B15 2TT, UK.
Email: l.j.hill@bham.ac.uk; c.thomas.4@bham.ac.uk

Funding information
Fight for Sight UK, Grant/Award Number: 5093/5094

Age-related macular degeneration (AMD) is the most common cause of blindness in the Western world and is characterised in its latter stages by retinal cell death and neovascularisation and earlier stages with the loss of parainflammatory homeostasis. Patients with neovascular AMD (nAMD) are treated with frequent intraocular injections of anti-vascular endothelial growth factor (VEGF) therapies, which are not only unpopular with patients but carry risks of sight-threatening complications. A minority of patients are unresponsive with no alternative treatment available, and some patients who respond initially eventually develop a tolerance to treatment. New therapeutics with improved delivery methods and sustainability of clinical effects are required, in particular for non-neovascular AMD (90% of cases and no current approved treatments). There are age-related and disease-related changes that occur which can affect ocular drug delivery. Here, we review the latest emerging therapies for AMD, their delivery routes and implications for translating to clinical practice.

1 | INTRODUCTION

Age-related macular degeneration (AMD) is the most common cause of visual loss in the developed world with ∼196 million people worldwide living with AMD, which is predicted to rise to 288 million by 2040 (Wong et al., 2014). Pathology associated with AMD occurs in the retina, a photosensitive membrane in the posterior segment of the eye which is responsible for vision, and in the choroidal blood vessels which supply nutrients and remove toxins to and from the retinal tissue. The neural retina is embryonically derived from the central nervous system (CNS) and therefore does not endogenously regenerate if injured or diseased. Thus, vision loss associated with retinal degeneration is irreversible.

AMD can be categorised into two forms: dry (non-vascular) AMD and advanced neovascular AMD (nAMD) (Figure 1). In the early stages of dry AMD there is chronic low-level inflammation, build-up of drusen deposits in the subretinal space and irreversible loss of retinal pigment epithelium (RPE) and photoreceptors in the macula, and subsequent progressive loss of central vision. In the late stages of dry AMD, RPE degeneration becomes confluent and vision loss is worsened, which is described as geographic atrophy (GA). Unfortunately, there are no treatments available for preventing sight loss in dry AMD patients, despite those individuals representing 90% of AMD cases. Patients are advised to partake in a healthy lifestyle, avoid smoking and to take anti-oxidant supplements. Restoration of immune homeostasis is one of the possible targets for emerging therapies to prevent sight loss in dry AMD patients. In approximately 10% of patients, AMD can progress to the more aggressive nAMD, which is associated with rapid loss of central vision and is characterised by abnormal choroidal blood vessel growth into the macula, called choroidal neovascularisation (CNV). These vessels are 'leaky' and there is excessive scar tissue. Currently, nAMD patients are treated with long-term, regular intravitreal injections of anti-vascular endothelial growth factor (**VEGF**) therapies (e.g., **bevacizumab** and **aflibercept**), aimed to reduce angiogenesis, oedema and stabilise vision loss. However, these therapies do not restore lost vision. Unfortunately, the long-term outcomes with anti-VEGF therapies are poor and two thirds of patients experience significant vision loss and almost all patients exhibit GA of the macula after 7 years (Rofagha et al., 2013; Xu et al., 2015). Additionally, long-term repeated intravitreal injections can lead to complications (uveitis, endophthalmitis, subconjunctival haemorrhage, elevated intraocular pressure and retinal detachment; Falavarjani & Nguyen, 2013), low adherence and high economic and societal costs and therefore long-lasting or minimally invasive alternatives are urgently needed for these patients.

Inflammatory responses to AMD are discussed in detail in other review articles (Copland et al., 2018; Handa et al., 2019; Perez & Caspi, 2015). Here, we will evaluate the latest therapies in development and clinical trials for treating AMD and discuss the delivery routes, with the overarching goal for clinical translation and patient treatment.

1.1 | Important considerations for AMD drug delivery

Many therapeutic agents are efficacious in attenuating disease pathogenesis in pre-clinical models of disease but often display poor clinical translation and fail in early human clinical trials. The most common route of delivery to the posterior segment of the eye is through localised intravitreal injections, where the therapeutic agent is delivered directly to the vitreous, which is in direct contact with the ganglion cell layer of the retina. However, intravitreal injections can be unpleasant for the patient and pose complication risks and often require multiple doses for effective treatment, resulting in a higher cumulative risk of complications. Immunotherapies can be delivered systemically through oral tablets or intravenous infusions, but systemic manipulation of the immune system can cause widespread side effects including infections of the CNS and activation of latent infections (Bascones-Martinez et al., 2014) and should be approached with caution. There is a huge unmet clinical need for sustained, less invasive alternatives for ocular drug delivery, which could include topical eye drop delivery, implantation of refillable slow-release implantable devices or single injection gene therapy. Despite long-lasting treatment with gene therapy, these therapies are expensive and permanent and therefore the pathophysiology needs to be evident and there needs to be high confidence that the therapeutic agent will treat the disease without adverse effects. There are obstacles to overcome when designing ocular delivery agents, including penetration of the ocular barriers, clearance of ocular fluid, tear film dilution and toxicity. Additionally, the delivery system needs to be biocompatible and remain optically clear within the vitreous to avoid interference with vision. Further, the expense of production and scale-up processes for the therapeutic agents need to be considered and financially affordable for patients. Repurposing drugs which have approval for use in other disease could be considerably cheaper than novel therapeutics. Figure 2 shows the age-related and disease-related changes in the eye which can affect drug delivery and biodistribution. Moreover, there are evident differences in pre-clinical model eyes compared to human eyes which will affect ocular drug delivery and will be discussed later in the review.

FIGURE 1 Pathophysiology of dry AMD and nAMD. In the healthy eye there is parainflammation and intact blood–retinal barriers (BRB). Dry (non-vascular) AMD involves low levels of chronic inflammation and the production of pathological lipid deposits called drusen and subretinal drusenoid deposits (SDD). Dry AMD can progress with widespread loss of photoreceptor (PR) and retinal pigment epithelium (RPE) cells, which is called geographic atrophy (GA). In a subset of patients (10%), dry AMD can progress into the more aggressive neovascular AMD (nAMD), characterised by abnormal choroidal blood vessel growth breaching Bruch's membrane into the retina, called choroidal neovascularisation (CNV) and imbalanced angiogenesis factors (pigment epithelium-derived factor, PEDF; and vascular endothelial growth factor, VEGF). However, development AMD is not always a linear progression and nAMD may occur in the absence of dry AMD pathology and nAMD can progress into GA. Abbreviations: IL, interleukins; ROS, reactive oxygen species

FIGURE 2 Age-related and disease-related changes to the eye which affect ocular drug delivery and biodistribution. There are numerous barriers for delivering drugs into the eye, including the tear film, cornea, sclera and the blood–retinal barrier (BRB). There are age-related changes in the eye and changes caused by AMD (dry and nAMD) pathology (grey boxes) which can affect drug biodistribution and pharmacokinetics (green boxes). Many elderly individuals have comorbidities including an artificial lens from cataract surgery which needs to be considered when designing therapeutic agents. Ageing leads to thickening of the vitreous which can adhere to the lens, affecting biodistribution of drugs. Additionally, there is a systemic age-related decline in the immune homeostasis and lower numbers of T and B lymphocytes. Changes specifically associated with AMD pathology include retinal pigment epithelium (RPE) and photoreceptor (PR) degeneration in dry AMD, but as the outer BRB breaks down there is potentially improved drug delivery of systemically administered therapeutic agents. In nAMD, there is abnormal blood vessel growth which are 'leaky' and lead to oedema and retinal scarring, which may reduce drug biodistribution. Abbreviations: CC, choroidal capillaries; DM, Descemet's membrane; E, endothelial cells; GCL, ganglion cell layer; HDL, high density lipoprotein; INL, inner nuclear layer; MC, Müller cells; ONL, outer nuclear layer; P, pericyte; SDD, subretinal drusenoid deposits; TJ, tight junctions

1.2 | Ocular barriers

The eye has complex barriers to maintain its immune privilege and prevent infection. These same barriers also pose difficulties for delivering therapeutic agents to the posterior segment of the eye (Figure 2). Non-invasive delivery by topical administration is a favourable alternative to intravitreal injections, but penetration of these ocular barriers remains a huge obstacle in the successful development of new treatments. Topically administered therapeutic agents can become diluted in the tear film and cleared through conjunctival blood vessels. These compounds need to transverse multiple corneal layers (epithelium, Bowman's membrane, stroma,

Descemet's membrane and endothelium) and there are tight junctions between the corneal epithelium which prevents hydrophilic molecules from penetrating the tissue. The stromal layer has highly organised and intertwined collagen fibres with a narrow pore size which prevents the penetration of larger molecules. Less than 5% of topically delivered treatments reach the anterior segment and considerably less reaches the retina. Additionally, there are drug transporters within the iris-ciliary body which actively eliminate the drug and reduce its bioavailability. The drug must then diffuse through the vitreous and penetrate the multiple retinal layers (ganglion cell layer, inner limiting membrane, inner nuclear layer, outer nuclear layer and outer limiting membrane) to reach the RPE

and the choroid at a therapeutic dose. The physical and biochemical barriers in the eye are massive hurdles to overcome but knowledge surrounding the features and interactions with drug delivery agents aid their development and successful translation.

Therapeutic agents delivered systemically must pass through the blood–retinal barrier (BRB). The outer BRB is formed from tight junctions between RPE, fenestrated choroid endothelial cells and Bruch's membrane and prevents invading pathogens, circulating cells and molecules from freely entering the retina as well as retinal antigens from entering into the circulation and activating the adaptive immune response. The inner BRB is composed of tight junctions between retinal capillary endothelial cells and regulates the movement of molecules into the inner retina. In normal tissue, the BRB is intact and endogenous 'alarmins' are unlikely to be detected by circulating or choroidal antigen presenting cells (APCs), but, in AMD the outer BRB can become disrupted and leaky as the RPE degenerate, allowing antigen movement and activation of the immune response. This barrier breakdown may also potentially allow access of systemically delivered therapeutic agents into the eye.

1.3 | Drug delivery to the ageing eye

AMD primarily affects the elderly population and aged eyes differ vastly from the eyes of juvenile patients. There are also structural and biochemical changes that occur in the aged human eye which can affect drug biodistribution (Figure 2), including a thicker, more fibrosis structure to the vitreous, associated with loss of hyaluronate and collapse of collagen fibres, leading to attachment to the lens and subsequent difficulty with drug biodistribution (Mains & Wilson, 2013). Cataract surgery and lens replacement are common for elderly individuals; which means that the physical and biochemical properties of an artificial lens need to be considered when designing therapeutic agents for AMD. Interestingly, the artificial lens could be utilised as a slow-release drug reservoir (Gonzalez-Chomon et al., 2011). In the cornea, there are fewer corneal endothelial cells and decreased stromal cell density, but thicker cornea epithelial and endothelial basement membranes (Gipson, 2013), thus, although increased amounts of a therapeutic agent might penetrate the outer endothelial layer, the thicker membranes may be more impermeable. Furthermore, there is a small decrease of ∼2.5% every decade in aqueous humour outflow and fewer trabecular meshwork cells (Alvarado et al., 1981; Diestelhorst & Kriegistein, 1992), which could affect drug clearance. Also, age-related thickening of Bruch's membrane (Bird, 1992) could hinder the delivery of systemically delivered therapeutics. With age, there is a general decline in the immune system, which increases the susceptibility to infections. Inflammaging is a term used to describe chronic, subclinical form of dysregulated parainflammation which occurs with age and contributes to the pathogenesis of multiple age-related diseases, including AMD. In asymptomatic 'healthy' individuals, there is a decrease in tear film stability, less tear production and higher levels of inflammatory markers (ICAM-1, IL-8 and MUC5AC) with age, demonstrating the persistent asymptomatic inflammatory state of inflammaging in the eye (Di Zazzo et al., 2019).

1.4 | The tissue microenvironment in eyes with AMD

The tissue microenvironment can alter the efficacy of drug penetration and pharmacokinetics (Nia et al., 2019). For example, photoreceptor and RPE atrophy associated with dry AMD will result in fewer cells and barrier breakdown and remaining cells may have reduced function. This could reduce efficiency of gene therapy, where cells are required to translate therapeutic proteins transfected with viral vectors. RPE atrophy can lead to BRB breakdown and may improve delivery of larger molecules from systemic administration. In nAMD there is excessive, abnormal choroidal angiogenesis, with leaky vessels and could lead to localised elevated fluid pressure and oedema. There is also extracellular matrix remodelling, fibrosis and scar formation which may reduce drug diffusion and penetration into the tissue.

2 | EMERGING THERAPIES AND THEIR DELIVERY FOR TREATING AMD

The delivery of treatments to the posterior segment are a priority in ocular research and have been reviewed in detail elsewhere (Del Amo et al., 2017). Here, we will focus on the delivery of therapies to the retina and choroid for treating AMD.

2.1 | Systemic immunosuppression

Systemic immunosuppression dampens down the immune response and treatments are often administered by intravenous infusion or subcutaneous injection. Interestingly in a large retrospective cohort study, systemic immunomodulatory therapies do not affect the risk of onset or progression of AMD in chronic kidney disease patients (Sandhu et al., 2018). These include the corticosteroid prednisone, antimetabolites such as methotrexate and azathioprine, calcineurin inhibitors cyclosporin and tacrolimus, mammalian target of rapamycin (mTOR) inhibitors sirolimus and everolimus, and T cell co-stimulation antagonist belatacept (Sandhu et al., 2018). However, the antimetabolite mycophenolate mofetil did demonstrate some protection against the conversion of dry AMD to nAMD in patients over 70, most likely through the downregulation of IL-1β by leukocytes and microglia, which would theoretically decrease CNV. In contrast, the study shows that everolimus might increase the risk of developing dry AMD (Sandhu et al., 2018). Furthermore, in a Phase II trial (NCT00304954) intravitreal injections of anti-VEGF therapy in combination with systemic immunosuppressive therapy (daclizumab or sirolimus) reduced the quantity of anti-VEGF injections needed to maintain stable visual acuity, with injections required per month reduced from 0.73 to 0.42 with daclizumab and 0.67 to 0.34 with

sirolimus after 6 months (Nussenblatt et al., 2010). Moreover, Alkahest, Inc. is developing an orally administered inhibitor of eotaxin (AKST4290), through blocking its binding to its G-protein coupled receptor CCR3, which plays important roles in inflammation, immune cell recruitment and neovascularisation. In the Phase II PHTHALO-205 trial (NCT04331730), AKST4290 was administered orally twice daily for 36 weeks, with loading doses of intravitreally injected aflibercept, in newly diagnosed nAMD patients. Results are expected in 2021. These studies indicate that some systemic immunosuppressive agents may be able to prevent the progression of early to late AMD and therefore could be a useful preventative or in combination with anti-VEGF therapies to reduce injection frequency.

2.2 | Anti-angiogenic therapies

2.2.1 | Anti-VEGF therapies

Anti-VEGF therapies are the most common treatment for nAMD. In 1989, VEGF was first reported as an angiogenic mitogen (Leung et al., 1989) (Keck et al., 1989) and was later shown to be elevated in the hypoxic retina of non-human primates injured with ischemic laser photocoagulation causing neovascularisation in the iris (Miller et al., 1994). There is a clear role for VEGF in abnormal angiogenesis in ocular disease with elevated levels of VEGF detected in the ocular fluid of patients with active neovascular eye disease (Aiello et al., 1994). Most approved therapies for nAMD target VEGF to prevent abnormal angiogenesis, which prevents further blood vessel growth and stabilises vision loss but does not restore lost vision or restore immune dysregulation associated with AMD.

The first anti-VEGF therapy developed for nAMD was pegaptanib (Macugen®, Eyetech Pharmaceuticals, Pfizer), a 28-base RNA aptamer which selectively binds and neutralises VEGF-165 isoform (Gragoudas et al., 2004) and was FDA approved in 2004 for ocular neovascularisation (Gonzales & Group VISiONCT, 2005). Pegaptanib has modifications of two 20 kDa polyethylene glycol (PEG) moieties to increase its vitreal half-life and modifications to prevent endonuclease and exonuclease degradation. Subsequently, bevacizumab (Avastin®, Genentech, Roche), a full-length humanised monoclonal antibody with two VEGF-A binding sites, was FDA approved for intravenous anti-angiogenic glioblastoma cancer therapy, showed efficacy in nAMD patients when delivered systemically (Michels et al., 2005) and via intravitreal injection (Rosenfeld et al., 2005). Later, ranibizumab (Lucentis ®) was developed, which is a modified version of bevacizumab and is an antibody fragment which binds and inhibits all identified VEGF isoforms, and was FDA approved for nAMD in 2006 for delivery via intravitreal injections (Rosenfeld et al., 2006). A further approved therapy targeting VEGF is the cytokine trap, aflibercept (Regeneron Pharmaceuticals). Aflibercept is a soluble fusion protein consisting of two extracellular cytokine receptor domains (VEGF-R1 and VEGF-R2) fused to Fc portion of human IgG1 and acts as a decoy receptor, sequestering VEGF

and preventing its receptor binding and downstream biological effects (Holash et al., 2002).

Anti-VEGF therapies are the current standard of care for preventing further vision loss in nAMD patients, although some patients are unresponsive to anti-VEGF therapies and still experience substantial vision loss. One third of nAMD patients displayed significant vision loss after receiving 7 years of VEGF-A blockade therapy and every patient displayed central retinal atrophy (Rofagha et al., 2013). This is consistent with pre-clinical rodent studies, with VEGF-A blockade causing cytotoxicity in the retina (Nishijima et al., 2007), highlighting the urgent clinical need for alternatives to intravitreal injected anti-VEGF therapies.

Current anti-VEGF therapies are biologics/proteins which require preservation of the tertiary and quaternary structures for their functionality and environmental factors including the temperature, pH and proteolytic enzymes can affect their structural integrity and function. The current therapies have short half-lives of between 5–8 days and hence require regular injections to prevent sight loss. A new anti-VEGF therapy, brolucizumab (Beovu®, RTH258, formerly ESBA1008), is a humanised single-chain antibody fragment which inhibits VEGF-A and is smaller (26 vs. 115 kDa for aflibercept and 48 kDa for ranibizumab) and has a longer half-life than aflibercept and ranibizumab, allowing for a higher dose and longer intervals between treatments (Holz et al., 2016). Theoretically, injecting a high drug concentration will create a large gradient from the vitreous to the retina and its lower molecular weight will support greater drug biodistribution. Thus, decreasing the number of injections required for equivalent clinical outcomes. Two Phase III trials, HAWK and HARRIER (NCT02307682, NCT02434328), showed non-inferiority of brolucizumab compared to aflibercept up to 48 weeks with 3-monthly injections and the reported adverse rates were similar (Dugel et al., 2017, 2020; Dugel, Singh, et al., 2021). Beovu® (Brolucizumab, Novartis) was FDA approved in October 2019 for nAMD treatment. Another alternative therapeutic is abicipar pegol (AGN-150998, Allergan plc/Molecular Partners), a designed ankyrin repeat protein (DARPins; a class of binding proteins which can aid protein–protein interactions) and specifically binds with high affinity to all soluble isoforms of VEGF-A. It has improved pharmacokinetic properties compared with current anti-VEGF treatments as it has a lower molecular weight (34 vs. 48 kDa) (Souied et al., 2014), higher target binding affinity (2 vs. 46 pM) and longer ocular half-life (≥13 vs. 7 days in the aqueous humour) compared with ranibizumab (Campochiaro et al., 2013; Krohne et al., 2012). In the Phase II REACH trial (NCT01397409), AGN-150998 showed comparable visual acuity and central retinal thickness up to 20 weeks when intravitreally injected at baseline and 4 and 8 month time points, compared to monthly ranibizumab intravitreal injections (Callanan et al., 2018; Souied et al., 2014). However, it failed to gain FDA approval in 2020 due to significant intraocular inflammation (8.9% to 15.4%) and unfavourable risk–benefit ratio (Khurana et al., 2020; Kunimoto et al., 2020). These smaller, longer lasting anti-VEGF biologics offer an exciting opportunity to increase the timeframe between intravitreal injections.

Topical therapies

Many currently approved anti-VEGF biologics are large peptides which also makes them less able to cross the ocular tissue membranes and makes non-invasive drug delivery by topical administration challenging. The development of an anti-VEGF therapy as a topical therapy is a viable alternative to intravitreal injections. Cell-penetrating peptides are a class of penetrating enhancing agents composed of a chain of positively charged peptides and can aid cellular and tissue penetration (Pescina et al., 2018). Pre-clinical studies successfully delivered anti-VEGF therapy, bevacizumab, as a topical administration to the retina and demonstrated equivalent efficacy to intravitreal injection in a mouse laser-induced CNV model (de Cogan et al., 2017). Acrizanib (LHA510; Alcon) is a low molecular weight VEGFR2 inhibitor which was delivered as a topical formulation but failed to show efficacy compared to anti-VEGF injections (Poor et al., 2018). Moreover, PAN-90806 is a VEGFR2 tyrosine kinase inhibitor (TKI) which is in development as a topical eye drop and delivered via the trans-scleral route to reach the retina and choroid. Initial Phase I/II trial studies (PanOptica, Inc. NCT0347937) showed reversible punctate keratopathy from off-target effects (PanOptica I, 2019), but the formulation has since been improved. PAN-90806 Phase I/II trials (PAN-01-102) showed safety and biological response in nAMD patients as a monotherapy, with 51% of patients on the study receiving only PAN-90806 eye drops with no rescue anti-VEGF injections (PanOptica I, 2019).

Sunitinib malate (GB-102) is a TKI which blocks signalling through pan VEGF receptors and has completed Phase I/IIa trials. It is currently in the Phase IIb ALTISSIMO trial (NCT03953079, Graybug Vision) to test the efficacy of GB-102 when intravitreally injected every 6 months. Sunitinib microparticles, which are coated with PLGA-PEG (to prevent pro-inflammatory effects), are in pre-clinical development and offer an exciting sustained release delivery system. These microparticles bind to melanin granules in the RPE and promote a depot for sustained release. They also have a surface treatment to promote self-aggregation in the vitreous to prevent interference with vision (Bhatt et al., 2019; GraybugVision, 2019a, 2019b; Tsujinaka et al., 2020; Ying et al., 2016). Furthermore, pazopanib is a multi-targeted TKI which inhibits VEGFR 1, 2, 3 and platelet derived growth factor (PDGF) signalling and has been developed as a topical formulation, with a reduction in CNV size in pre-clinical models (Takahashi et al., 2009; Yafai et al., 2011). In Phase II trials with 5 mg ml^{-1} eye drops, applied 3 times daily, there was improved best-corrected visual acuity (BCVA) in patients with sub-foveal CNV secondary to AMD (Danis et al., 2014). However, pazopanib failed to meet its primary endpoints in a Phase IIb trial at Week 52, it was non-inferior to ranibizumab and did not reduce the number of ranibizumab injections by 50% (Csaky et al., 2015). Another therapeutic agent in development is squalamine lactate, which inhibits angiogenesis induced by VEGF, PDGF and basic fibroblast growth factor (bFGF) by a novel intracellular mechanism and inhibits ocular neovascularisation in pre-clinical models (Ciulla et al., 2003). Originally, squalamine lactate was developed as an intravenous drug and demonstrated a biological effect, dose response and visual acuity benefit in Phase II trials, but due to rapid clearance and impractical delivery it was not investigated further. Ohr Pharmaceuticals launched a proprietary formulation of 0.2% squalamine lactate eye drops (OHR-102), which have improved trans-scleral permeability and increased retention at the target choroid tissue and have completed a Phase II IMPACT trial (NCT01678963) in patients with all types of naïve neovascular lesions. Patients were randomised to receive a ranibizumab intravitreal injection at baseline followed by OHR-102 eye drops twice daily or vehicle and received monthly intravitreal injections of ranibizumab as needed. This trial demonstrated a trend towards better visual acuity in patients receiving OHR-102 eye drops after 36 weeks of treatment, particularly in a subgroup of patients who had classic lesions and CNV less than 10 mm^2. This patient subgroup was specifically recruited for Phase III trials (MAKO trial; NCT02727881), which unfortunately failed to meet the primary endpoint and showed no efficacy analysis.

Sustained release implants

An alternative method for sustained delivery is through surgical non-biodegradable implants. These implants can be refilled in the clinic to allow for long-term delivery of anti-VEGF or other therapeutic agents. Genentech© are currently developing an implantable, reservoir based, refillable implant called the Ranibizumab Port Delivery System (PDS) (RPDS) for prolonged release to deliver ranibizumab for nAMD. This system has entered Phase II clinical trials (LADDER trial; NCT02510794), which has reported that sustained release of 100 mg ml^{-1} of ranibizumab delivered via the RPDS induces similar visual acuity outcomes to monthly ranibizumab intravitreal injections and has a median refill time of 15 months (Campochiaro et al., 2019). However, there were more adverse events associated with surgical implantation of the device compared to intravitreal injections, with 179 of patients (8.9%) with RPDS implantation developing serious adverse events including vitreous haemorrhage. Two Phase III trials have launched, ARCHWAY (NCT03677934) and PORTAL (NCT03683251) trials, to compare monthly ranibizumab intravitreal injections with the RPDS with refill every 24 weeks for 144 weeks. Preliminary results from the ARCHWAY trial demonstrates 98.4% of patients with the RPDS maintain vision for 6 months without additional treatments and achieved equivalent visual outcomes compared to monthly ranibizumab intravitreal injections (Campochiaro et al., 2019). Another nAMD treatment which has undefined mechanisms, RO-7250284 (Hoffmann-La Roche; NCT04567303) has entered Phase I trials and is delivered via intravitreal injections and the PDS, demonstrating the opportunity to use this slow-release implantable device for other therapeutics. These studies demonstrate the development of therapeutic agents with a longer timeframe between treatments. This is likely to improve patient compliance and reduce pressure on healthcare systems to administer regular intravitreal injections, although the overall lifetime of the PDS needs to be further explored.

Encapsulated cell technology

NT-503-3 is a sustained release device containing genetically engineered RPE cells which produce anti-VEGF therapy and is

delivered by an encapsulated cell technology (ECT) implant. Unfortunately, a Phase II trial (Neurotech Pharmaceuticals; NCT02228304) was terminated early due to a high rate of rescue events (Kiss, 2016). The same ECT was used to delivery an implantation containing genetically modified human RPE cells producing sustained ciliary neurotrophic factor (CNTF) for treating GA. NT-501 (Renexus®, NT-501, Neurotech Pharmaceuticals; NCT00063765, NCT00447954), produces continuous CNTF production for >5.5 years since implantation (Kauper et al., 2013). NT-501 has also been pre-clinically investigated as a delivery agent for CR2-Fh (Annamalai et al., 2018). Renexus® has been FDA approved for retinitis pigmentosa and macular telangiectasia and is in fast track for dry AMD.

Gene therapy

Gene therapy could offer an alternative for long-term delivery of anti-VEGF treatments. A vector containing the gene which encodes for a VEGF monoclonal antibody fragment can be injected as a one-time subretinal treatment to provide a lifelong continuous supply to the choroid and retina and reduce abnormal angiogenesis and CNV. RGX-314, a NAV AAV8 vector encoding for soluble anti-VEGF protein is currently in ongoing Phase II clinical trials for nAMD (Regenxbio Inc. NCT03066258, AAVIATE trial NCT04514653) and is delivered into the suprachoroidal space using a microinjector. Furthermore, ADVM-022 (Adverum Biotechnologies Inc.), an AAV vector 7 m8-aflibercept in the OPTIC trial (NCT03748784) displayed long-term durability of >1 year from a single intravitreal injection with no rescue injections required in the higher dose 6×10^{11} vector genomes, but greatest improvements from 2×10^{11} vector genomes group (n = 9) with mean CRT change from baseline of -137.8 mm and mean BCVA gain from baseline of $+6.8$ letters at 20 weeks (Khanani, Kiss, et al., 2020), with the full study completion expected in 2022. An AAV2 vector expressing an VEGF neutralising protein called SFLT01, which is a novel fusion protein consisting of the VEGF binding domain of the human VEGFR1/Flt-1 (hVEGF-R1) fused to the Fc portion of human IgG through a polyglycine linker has shown a positive results when delivered by subretinal injection in a transgenic mouse model of retinal neovascularisation (trVEGF029 mice), with a reduction in fluorescein leakage from retinal vessels and improved retinal function (Lai et al., 2009). A single subretinal injection of 1×10^{11} vector genomes in Phase I and IIa trials (Adverum Biotechnologies Inc. NCT01494805) showed no serious adverse effects or systemic safety concerns and 12 (57%) patients in the rAAV.sFLT-1 group maintained or improved visual outcomes compared to only 4 (36%) in the control group (Constable et al., 2016; Rakoczy et al., 2015). However, gene therapies are very expensive and the treatment provides lifelong production of protein which cannot be turned off. Therefore, it must be shown that this therapy can improve the disease in the long-term without adverse effects. As discussed earlier, the long-term delivery of anti-VEGF therapies can induce poor outcomes, with two thirds of patients experiencing significant vision loss and almost all patients developing GA of the macular after 7 years (Rofagha et al., 2013; Xu et al., 2015), indicating long-term delivery of anti-VEGF agents could be detrimental.

Anti-VEGF and other pathways

There are newer therapeutic agents which target VEGF, in combination with other pathways shown to drive AMD pathology. For example, IBI302 (Innovent Biologics Co. Ltd) is a novel bispecific decoy receptor fusion protein designed with domains to inhibit both VEGF and the complement cascade and are connected by the Fc region of human immunoglobulin (Ren et al., 2016). IBI302 has shown anti-angiogenic and anti-complement effects and positive pharmacokinetic profiles in non-human primates (Ren et al., 2016) and is in ongoing Phase I dose escalation trials for nAMD (NCT04370379; expected June 2021). Furthermore, BI 836880 (Boehringer Ingelheim), a humanised bispecific nanobody which targets VEGF and angiopoietin-2 (Ang2), a growth factor involved in angiogenesis, is in ongoing Phase I trials (NCT03861234; expected October 2021). Hoffmann-La Roche have also shown positive outcomes with faricimab (RO6867461, RG7716; Hoffmann-La Roche), which simultaneously blocks VEGF and Ang2. In the STAIRWAY Phase II trial (NCT03038880), 6 mg of faricimab was intravitreally injected every 12 or 16 weeks which resulted in the maintenance of initial vision and anatomical improvements, comparable with monthly ranibizumab injections at 52 weeks (Khanani, Patel, et al., 2020). These results suggest a role for simultaneous neutralisation of Ang2 and VEGF-A in providing sustained efficacy through extended durability. However, nesvacumab-aflibercept (ONYX study), an aflibercept co-formulated with Ang2 antibody, failed to meet the clinical endpoint at Week 36 in a Phase II trial (Regeneron, 2017).

Treatments that are delivered by oral administration and target VEGF are also in development. An oral angiogenesis inhibitor which targets VEGF receptors, PDGFRs and colony stimulating factor 1 receptors (CSF1R) has shown positive results in a pre-clinical, laser-induced CNV rat model, with high concentrations of CM082 reaching the eye (173 ± 58 ng g^{-1}) which is comparable to systemic plasma concentrations (197 ± 73 ng ml^{-1}), thus, demonstrating potentially effective BRB penetration. The size of the laser-induced CNV was also significantly reduced compared to vehicle. CM082 has entered Phase II trials (X-82; Anew Pharma Inc.; NCT03710863) and will be taken orally twice daily for 2 weeks followed by a 2-week interval, in 4-week cycles.

2.2.2 | Anti-PDGF agents

PDGF is an angiogenic factor which has been targeted for nAMD therapies. HL-217 is a synthetic inhibitor of PDGF, which has shown promising results at reducing CNV size in pre-clinical rodent studies with topical application (Kim et al., 2015), has completed Phase I trials (Hanlim Pharm. Co., Ltd. NCT03650608, NCT03648346) and has entered Phase II trials (EudraCT number: 2019–000642-35). Pegpleranib/Fovista (E10030; Ophthotech) is a PEGylated DNA aptamer with selective anti-PDGFβ action and has completed successful Phase I and II trials (NCT01089517) (Jaffe et al., 2016, 2017). In Phase III trials (NCT01940900), 1.5 mg per eye of Fovista was intravitreally injected in combination with 0.5 mg of ranibizumab and

at 12 months showed no significant differences between the combination therapy and ranibizumab alone, leading to premature termination of the study (Dunn et al., 2017; Rosenfeld & Feuer, 2018). Moreover, rinucumab-aflibercept, an aflibercept (anti-VEGF) co-formulated with rinucumab (an anti-PDGF-Rβ antibody) failed in its Phase II clinical trial (CAPELLA STUDY) due to no additional visual or anatomical improvements with the combination therapy, compared with aflibercept monotherapy at 3 months (Heier, Wykoff, et al., 2020). Furthermore, **regorafenib** which inhibits VEGF-R 2/3 and PDGFR was terminated in a Phase IIa trial (DREAM study) due to a loss of 2.4 EDRS letters at 12 weeks (Joussen et al., 2019). The lack of therapeutic efficacy with anti-PDGF agents has been disappointing and other avenues should be explored.

2.2.3 | Anti-FGF aptamers

Fibroblast growth factor 2 (FGF-2) inhibitors can block angiogenesis and retinal scar formation. An anti-FGF-2 aptamer (RBM-007) inhibited FGF2-induced angiogenesis, laser-induced CNV and retinal fibrosis (Matsuda et al., 2019) and pharmacokinetic studies in the rabbit vitreous revealed high and relatively long-lasting profiles, compared with approved anti-VEGF drugs (Matsuda et al., 2019). RBM-007 is an FGF-2 aptamer in phase II TOFU trial (Ribomic USA Inc. NCT04200248) and is administered as four monthly intravitreal injections alone or in combination with aflibercept (expected end date is June 2021). Furthermore, RemeGen Ltd have ongoing Phase II clinical trials (NCT04270669) with intravitreal injections of RC-28, a recombinant dual decoy receptor IgG1 Fc-fusion protein that blocks both VEGF and FGF-2. These newly developed therapeutic agents targeting FGF-2 could offer a vital alternative for anti-VEGF unresponsive patients and also target retinal scar formation.

2.2.4 | Amyloid-β targeted antibodies

Amyloid β (Aβ) aggregation in the brain are a fundamental characteristic of Alzheimer's disease pathogenesis and has been implicated in the development of AMD, due to their similarities with lipid depositions. Aβ deposits might be associated with more advanced AMD, with an association of Aβ accumulating in retinal tissue with moderate to high drusen levels (Anderson et al., 2004). Aβ is also present in nAMD and may contribute to late stage nAMD pathogenesis. In cultured human RPE cells, Aβ affected the angiogenesis-related factors, inducing VEGF and decreasing pigment epithelium-derived factor (PEDF) protein expression (Yoshida et al., 2005) and stimulating cellular senescence and a pro-inflammatory microenvironment (Cao et al., 2013). Genetically modified mice with **neprilysin** deficiency, which induces increased Aβ depositions, displayed AMD-like pathology including subretinal formation of basal deposits and RPE degeneration, but, these mice did not develop CNV up to the 27 month study endpoint (Yoshida et al., 2005), suggesting Aβ depositions may induce early but not late AMD. Systemic

delivery of Aβ-therapy could be a potential viable route of administration for preventing vision loss in AMD patients as systemic Aβ-therapy rescued visual defects in ApoE4-HFC transgenic mice (Ding et al., 2008;, 2011). Despite positive results in pre-clinical studies, Phase II clinical trials with anti-Aβ monoclonal antibodies from Pfizer (RN6G, Pf-04382923; NCT01577381) and GlaxoSmithKline (GSK933776; NCT01342926) were ineffective for dry AMD (Berger et al., 2013). RN6G was administered as an intravenous 30-min infusion (2.5–15 mg kg^{-1}), but the study was terminated early due to an organisational decision. GSK933776 was also delivered by intravenous infusion at comparable doses (3–15 mg kg^{-1}) but did not slow the rate of GA enlargement compared to placebo and there were no clinically meaningful differences in visual function over 18 months (Rosenfeld, Berger, et al., 2018). A small peptide inhibitor which selectively targets misfolded Aβ aggregations, GAL-101, and delivered as a topical formulation 3× daily for 1 month reduced complement C3b in pre-clinical studies (Hermann, 2019) and has successfully completed Phase I trials for GA (RemeGen Ltd; NCT03777254). Together, these studies suggest that Aβ depositions could play an important role in AMD pathogenesis, but systemic delivery of anti-Aβ monoclonal antibodies have been ineffective at preventing disease progression in dry AMD, but topical application of a selective small peptide inhibitor might be successful, and may suggest that Aβ might not be the primary cause driving pathology in AMD.

2.3 | Immunotherapies

Immunotherapies, where the immune response is stimulated or suppressed to treat disease, are an exciting avenue for treating AMD as they provide the promise to treat AMD pathology at an earlier stage and halt disease progression through restoring immune homeostasis, with downstream pathology prevented. Low-level inflammation (parainflammation) is an important immunological mechanism for maintaining tissue homeostasis and for monitoring tissue dysfunction. However, if the optimal homeostatic threshold is not restored and there are excessive parainflammatory responses, then this can result in chronic inflammation and subsequent tissue dysfunction (Copland et al., 2018). Immunomodulation through interleukins, interferons or microglial-targeting therapies could be useful as therapeutics to restore immune homeostasis and resolve chronic inflammation in AMD.

2.3.1 | Interleukins

Interleukins are cytokines which are secreted from T cells, monocytes, macrophages and endothelial cells and their main role is to promote the growth and differentiation of haematopoietic cells and T and B lymphocytes. Interleukins are strongly suggested to aid the restoration of immune homeostasis in dry AMD and to prevent the conversion to the more aggressive nAMD. These cytokines may also present a suitable alternative for anti-VEGF unresponsive

patients in nAMD. Rather than targeting anti-inflammatory mechanisms, the promotion of inflammation may help tissue repair, instead of hindering the repair process and leading to persistence of disease.

Interleukin-18

The **NLRP3** (NOD-, LRR- and pyrin domain-containing protein 3) inflammasome may be able to 'sense' drusen in human AMD donor eyes and cleave pro IL-1β and **IL-18** into their active forms to induce an inflammatory response and pyroptosis (Doyle et al., 2012). As well as raised IL-18 levels associated with AMD pathology, exogenous mature interleukins may be protective and used an as immunotherapy. In a laser-induced CNV mouse model, local and systemic delivery of exogenous mature recombinant IL-18 effectively reduced CNV development and was effective when intravitreally injected alone and as an adjunct with anti-VEGF therapy (Doyle et al., 2014). Additionally, IL-18 immunotherapy delivered as intravitreal injections demonstrated tolerability and efficacy in non-human primates (Doyle, Lopez, Celkova, et al., 2015). IL-18 can induce inflammasome activation and RPE degeneration (Ijima et al., 2014) suggesting that IL-18 could potentially exert detrimental rather than beneficial effects. Patients with the auto inflammatory diseases, systemic juvenile idiopathic arthritis and adult-onset Still's disease, have chronically elevated systemic IL-18 but do not develop macular degeneration or CNV (Canna et al., 2017), suggesting that long-term IL-18 immunotherapy would not be detrimental to the retina. However, recombinant IL-18 did not protect against CNV development and induced further RPE degeneration (Hirano et al., 2014). These discrepant results are likely to be due to the use of alternative recombinant mouse IL-18 which has a lower bioactivity compared to the GlaxoSmithKline (GSK) generated mouse IL-18 (SB-528775) which was used in the original studies (Doyle et al., 2014; Doyle, Lopez, Celkova, et al., 2015; Doyle, Lopez, Humphries, et al., 2015). SB-485232 has shown positive safety results when injected systemically into 170 cancer patients (NTC00107718), with no safety concerns or adverse visual effects reported (Robertson et al., 2008). This suggests that immunotherapy with systemic IL-18 does not cause vision loss and is safe to use in humans. The anti-angiogenic effects of IL-18 in nAMD are supported by further independent studies (Marneros, 2013; Shen et al., 2014). Collectively, these studies suggest that IL-18 could be a good adjunctive immunotherapy alongside anti-VEGF therapy to treat nAMD and will offer a valuable alternative therapy for anti-VEGF unresponsive patients.

Interleukin-33

IL-33 has also been proposed to reduce neovascularisation in laser-induction CNV mouse models (Theodoropoulou et al., 2017). IL-33 is unique because it is active without caspase cleavage and does not require inflammasome activation for secretion and bioactivity. It behaves as an 'alarmin' and is released following cellular damage and biomechanical overload (Lamkanfi & Dixit, 2009). It signals through a heterodimeric receptor consisting of **ST2** receptors and IL-1R accessory protein, and the membrane form of ST2 is expressed on many immune cells (Liew et al., 2016). In cell cultures, the recombinant form of IL-33 (AA 112–270) reduces angiogenesis through the direct inhibition of human choroidal fibroblasts and choroidal endothelial cells, both of which express a high level of ST2 receptors (Theodoropoulou et al., 2017). In addition, in a laser-induced CNV mouse model delivery of recombinant IL-33 through intravitreal injections reduced the lesion size (Theodoropoulou et al., 2017), suggesting IL-33 could be a promising treatment for patients who are unresponsive to anti-VEGF therapies. Furthermore, IL-33$^{-/-}$ mice demonstrated elevated retinal degeneration and gliosis following a retinal detachment injury compared to controls, with sustained subretinal inflammation from infiltrating macrophages (Augustine et al., 2019). Conversely, endogenous IL-33 can promote an inflammatory response and recruit monocytes in a phototoxic retinal degeneration model, which results in photoreceptor degeneration (Xi et al., 2016). These studies demonstrate the opposing effects of endogenous and exogenous IL-33 and should be considered in future therapeutic developments. IL-33 might also be offered as a valuable therapeutic for restoring tissue homeostasis in dry AMD patients. The delivery of exogenous recombinant IL-33 protein using intravitreal injections also demonstrated protection against RPE degeneration and maintained metabolic retinal homeostasis in CFH$^{+/-}$ aged mice fed on a high fat diet (Clare et al., 2020), suggesting further evidence for IL-33 preventing AMD progression and an exciting avenue.

Interleukin-10

IL-10 also has a role in AMD pathogenesis in mice, with increased protein expression driving the activation of **STAT3** signalling in senescent macrophages and the promotion of vascular proliferation and angiogenesis (Nakamura et al., 2015). Inhibition of the IL-10 receptors using a neutralising antibody against the **IL-10-R1** reversed this disease phenotype, with a fivefold reduction in CNV volume compared to control mice (Nakamura et al., 2015). Furthermore, intravitreal injection of STAT3-deficient macrophages into the eyes of aged mice attenuated the CNV area (Nakamura et al., 2015), suggesting that M2 macrophage specific targeting of STAT3 signalling may be a novel therapy for treating nAMD. A pretreatment of low-dose lipopolysaccharide (LPS) delivered by intraperitoneal injection daily from 4 days before laser injury reduced the CNV lesion size by ∼65% compared to control mice. This was correlated with raised IL-10 protein in the serum and elevated IL-10 mRNA in peritoneal macrophages and peritoneal injection of anti-IL-10 antibody reversed this protective effect (Matsumura et al., 2012), indicating this pathology was IL-10-dependent and that IL-10 could be delivered systemically as a therapeutic agent for preventing neovascularisation in AMD.

2.3.2 | Interferon immunotherapy

Interferons are proteins produced in response to viral infections and can boost the immune systems response. **Interferon α-2a (IFN-α-2a)** is an anti-angiogenic molecule, which reduces abnormal angiogenesis in retinal diseases in pre-clinical models. Nonetheless, clinical trials

demonstrate that systemic delivery of IFN-α-2a or IFN-α-2b were not advantageous in nAMD patients and may be more harmful than beneficial (Lewis et al., 1993). This lack of effect could be explained by high levels of neutralising antibody against IFN-α-2a in the serum of a proportion of patients (Ross et al., 2002) and interferon treatment may have a more localised effect if delivered into the eye. There are several anti-angiogenic interventions available or in development, and it is thus unlikely that further investigation into the use of interferons for treating nAMD will be justified.

2.3.3 | Microglia targeting immunotherapies

In the healthy retina, microglia play an important role in immune surveillance and preservation of tissue integrity. After an injury, they proliferate and migrate to the damage site to phagocytose cell debris and release neuromodulatory factors to promote tissue repair. Controlled microglial activation for short periods can be protective, however, if this becomes chronic and prolonged it can cause tissue damage. Resident retinal microglia could be targeted therapeutically to prevent neovascularisation and retinal degeneration (Akhtar-Schafer et al., 2018).

Interferon-β (IFN-β), which can prevent activation of microglia, has been proposed to have an immunomodulatory effect and reduces laser-induced CNV in mice when delivered via systemic administration (Luckoff et al., 2016). Furthermore, another potential therapeutic in pre-clinical development are translocator protein 18 kDa (TSPO) ligands. TSPO protein expression is highly induced, predominantly in activated microglia. Synthetic TSPO ligands were used therapeutically as immunoregulators to dampen microglial reactivity and reduce pathological outcomes. The TSPO ligand, XBD173, was systemically administered in a mouse model of white light damage, which leads to photoreceptor loss and outer nuclear layer thinning and showed reduced microglial accumulation in the outer retina and significantly reduced photoreceptor cell death (Scholz et al., 2015). Moreover, in a laser-induced CNV mouse, microglial-specific TSPO-KO and treatment with TSPO ligand XBD173 diminished mononuclear phagocyte reactivity and neovascularisation (Wolf et al., 2020). These studies highlight the potential of TSPO as a therapeutic agent for AMD and its administration via systemic routes.

2.4 | Complement system-targeting therapies

The complement system is a subsection of the innate immune response and is composed of soluble and surface proteins which modulate the host defence against infection and antigen-specific immune and inflammatory responses. Complement proteins enhance the ability of antibodies and phagocytic cells to attack pathogens, clear damaged cells and promote inflammation. The complement system is chronically active at low levels in the eye and complement components are present in the normal composition of tears, suggesting that it may act as an ocular primary

defence mechanism (Willcox et al., 1997). The dysregulation of the complement pathway plays an important role in the pathogenesis of AMD and can be targeted to restore immune homeostasis (Wu & Sun, 2019).

2.4.1 | Complement components

Complement components and activation products, for example C3a, C5a and the membrane attack complex (MAC), have been localised to drusen deposits in post-mortem AMD eyes (Johnson et al., 2001). Furthermore, the polymorphism rs2230199 (Arg80Gly) in the complement protein C3 gene is associated with an elevated risk of developing AMD (Yates et al., 2007). The generation of the MAC is critical for the development of CNV, demonstrated by a lack of CNV development from laser-induced injury in C3$^{-/-}$ mice and mice treated with anti-C6 treatments (Bora et al., 2005). Additionally, in the absence of MAC formation, the release of angiogenic factors including VEGF, TGF-β2 and β-FGF was inhibited (Bora et al., 2007). This study highlights that an anti-C6 or anti-C3 antibody therapy could be a potential therapeutic target for the treatment of nAMD. NGM Biopharmaceuticals Inc. have developed a humanised IgG1 monoclonal antibody (NGM621) which potently inhibits C3 and is in Phase II CATALINA trial for GA (NGM Biopharmaceuticals; NCT04465955), with results expected in 2023. Patients with GA secondary to AMD will receive a single intravitreal injection every 4 or 8 weeks and the GA lesion area will be measured by fundus autofluorescence at 48 weeks.

The complement activation products C3a and C5a could also be potential therapeutic targets. C3a and C5a are present in drusen deposits in human donor eyes and in the choroid of laser-induced CNV mice (Nozaki et al., 2006), suggesting possible roles in both dry AMD and nAMD. Zimura™ (also called avacincaptad pegol; Ophthotech, INVERIC Bio Inc.) is an anti-C5 aptamer, which inhibits C5 cleavage into C5a and C5b, thus decreasing MAC formation. Zimura™ has completed a Phase II/III trial (GATHER1 study, NCT02686658) in GA patients, with a significant reduction in GA growth in eyes receiving intravitreal injections of avacincaptad pegol (2 or 4 mg) over 12 months (Jaffe, Westby, et al., 2021) and has entered Phase III trial to confirm efficacy (GATHER2 study, NCT04435366). Zimura™ was also tested in Phase II trials in combination with Lucentis for nAMD patients, but despite promising results Ophthotech have decided not to continue this pipeline for nAMD. Moreover, Alexion Pharmaceuticals have completed Phase II trials in 2013 (COMPLETE trial, NCT00935883) with systemic administration of eculizumab, a monoclonal antibody against C5a and C5b. Patients with GA secondary to AMD received either 600 or 900 mg of the therapeutic agent by intravenous infusion over 30 min each week for 4 weeks followed by 900 or 1200 mg every 2 weeks until Week 24. Patients received a follow up to 6 months after the final treatment. Unfortunately, systemic complement inhibition using eculizumab did not reduce the growth rate of GA significantly, but was well tolerated and there was some significant correlation between low-luminance

deficit and the progression of GA over the 6 months (Yehoshua et al., 2014).

Tesidolumab (LFG316) is a human immunoglobulin G1 (IgG1) monoclonal antibody directed against the complement pathway protein C5 and is in Phase II trials for GA (Novartis Pharmaceuticals; NCT01527500) (Novartis, 2015). Novartis also have a properdin/complement factor B (CFB) (positive regulator of the alternative complement pathway) inhibitor which prevents the formation of early (C3 cleavage) and late (C5 and the MAC) activation products in the complement cascade, which is in Phase II trials for GA as a monotherapy and also in combination with LFG-316 (Alcon Research, Novartis Institutes for Biomedical Research; NCT02515942).

The formation of the MAC may be associated with decreased complement factor H (CFH) and increased CFB in the RPE and choroid in a laser-induced CNV mouse model (Bora et al., 2006). Sub lytic MAC can have immunomodulatory roles, including induction of IL-6, IL-8, CCL2 and production of angiogenic VEGF (Lakkaraju et al., 2014). In addition to a potential protective anti-angiogenic role, the inhibition of MAC formation could prevent RPE death and GA associated with dry AMD. CD59 is a complement regulatory protein (CRP) which inhibits MAC formation and CNV development. In $CD59a^{-/-}$ C57Bl/6 mice received laser-induced CNV and the CNV lesion developed earlier in the disease process compared to wild-type mice (Bora et al., 2007). Intraperitoneal or intravitreal injections of a recombinant, soluble mouse CD59a-IgG2a fusion protein administered 24 h before laser injury inhibited CNV development at 7 days (Bora et al., 2007), by inhibiting the formation of MAC and reducing downstream release of angiogenic factors such as VEGF, β-FGF and TGF-β2 (Bora et al., 2007). Recombinant forms of CD59 could be used as a potential therapy to treat nAMD and target later in the complement pathway and, thus, will not interfere with early complement activation which has vital roles in the host response to infection and facilitating tissue healing. Gene therapy could be used to induce lifelong supply of the therapeutic agent and has shown promising results at reducing RPE degeneration in vitro (Ramo et al., 2008) and attenuating laser-induced CNV in mice (Cashman et al., 2011). AAVCAGsCD59 (HMR59), a viral vector for the soluble CD59 has completed a Phase I trial for GA and a trial for nAMD is ongoing (Hemera Biosciences Inc. NCT03144999, NCT03585556). Janssen Pharmaceuticals, Inc., has recently acquired the rights to HMR59 gene therapy.

2.4.2 | Complement factors

Complement factors could also be targeted therapeutically. Allelic variants in CFH are major risk factors in AMD development. For example, a polymorphism of tyrosine to histidine at position 402 is associated with a five to seven-fold increased risk of developing AMD (Hageman et al., 2005). Aged (90 weeks old) $CFH^{-/-}$ mice on a high fat, cholesterol enriched diet spontaneously develop AMD-like retinal phenotypes, such as photoreceptor dysfunction, C3

depositions and Bruch's membrane thinning (Coffey et al., 2007). Gemini Therapeutics have initiated Phase I trial with a full-length recombinant human CFH, GEM103, for treating dry AMD in patients who have known CFH mutations (Gemini Therapeutics, Inc.; NCT04246866).

Gene therapies are at the forefront of research and translation into patients as they offer permanent, lifelong delivery of the therapeutic agent. However, they must be used with caution due to their expense, permanent effect and, in the case of complement proteins, an unproven mechanism from multiple failed trials. A novel specific antisense oligonucleotide targeting the CFB gene (coding for complement factor B) IONIS-FB-L_{Rx} (also known as ISI 696844; Ionis Pharmaceuticals, Inc.) could be used to reduce the levels of circulating CFB. IONIS-FB-L_{Rx} has shown promising clinical safety, pharmacokinetic and pharmacodynamic activity in a Phase I trial (ANZCTR registration number: ACTRN12616000335493) and is in ongoing Phase II trials (GOLDEN study; NCT03815825) to determine if a subcutaneous injection every 4 weeks will reduce the GA area growth over 12 months (Jaffe, Sahni, et al., 2020), with results expected in 2022. Systemic targeting of complement should proceed with a level of caution as it has important roles in immune surveillance and inhibition could induce broad, systemic side effects, including increased risk of infection.

Moreover, Gyroscope Therapeutics is developing GT005, a novel recombinant non-replicating AAV vector encoding for the human complement factor I (CFI) protein, which is a negative regulator of the alternative complement pathway. In pre-clinical models, GT005 showed dose-dependent CFI expression in the mouse eye following subretinal injections, specifically in the RPE (Ellis et al., 2020) and led to dose-dependent and significant reductions in CNV size in a mouse CNV model. There were no adverse systemic effects found in mice or non-human primates. These positive pre-clinical studies initiated a Phase I/II clinical trials for GA secondary to dry AMD (FOCUS; NCT03846193 and EXPLORE; NCT04437368), with no safety concerns to date (Ellis et al., 2020). In the Phase I/II FOCUS trial, GT005 was delivered using the Orbit™ Sustained Delivery System (SDS), which allows delivery to the subretinal space without the need for a vitrectomy (removal of the vitreous) or retinotomy (a hole in the retina). This technology is also used to deliver cell therapies which will be discussed later in the review.

There have been positive results with an antigen-binding fragment of the humanised monoclonal antibody against complement factor D (CFD), which selectively inhibits CFD and blocks the alternate complement pathway, lampalizumab (also known as RO5490249; Genentech, Hoffmann-La Roche). Lampalizumab is in Phase II clinical trials (MAHALO; NCT01229215) for GA secondary to AMD (Yaspan et al., 2017). The progression of GA lesion size was 20% lower with monthly 10 mg lampalizumab compared to sham, in particularly with carriers of CFI with 44% reduction in progression of GA area (Yaspan et al., 2017). This led to two Phase III trials, the CHROMA and SPECTRI trials (NCT02247479, NCT02247531), where patients received 10 mg of intravitreally injected lampalizumab every 4 or 6 weeks, but there was no

meaningful differences in the GA lesion area and thus the trials were terminated early due to lack of efficacy at 12 months (Holz et al., 2018). This was likely due to selective sub-optimal inhibition of only the alternate complement pathway and minimal effect on the classical and lectin pathways.

Lampalizumab, along with other complement-based treatments, could be targeted too late in AMD pathogenesis to prevent GA development. It is likely that complement activation precedes RPE degeneration and atrophy of the choriocapillaris and that other damaging biochemical pathways which are activated are independent from the original complement over-activation by the time of late therapeutic intervention in these trials. This suggests that complement-targeting treatments may be more effective at an earlier disease stage.

2.5 | Senotherapeutics

Senescence is a biological state whereby a cell permanently halts cell division. These cells accumulate with age and secrete senescence-associated secretory phenotype (SASP) proteins (i.e., pro-inflammatory factors, pro-fibrotic factors, growth factors and proteases) which affects the tissue microenvironment and can induce senescence in neighbouring cells. The role of senescence in AMD is emerging, with elevated expression of senescence markers p53 and p21 and phospho-p38 MAPK levels in AMD (Lee et al., 2021). Senotherapeutic agents are senolytics which selectively kill senescent cells. UBX1967 and UBX1325 (Unity Biotechnology, Inc.) are senolytic potent small molecule inhibitors of the Bcl-2 family, are in an investigational new drug heading towards human trials (Unity Biotechnology I, n.d.). Although there are no therapies in trials for AMD currently, senotherapeutics offers a promising area for targeting AMD pathophysiology from a new avenue (Lee et al., 2021).
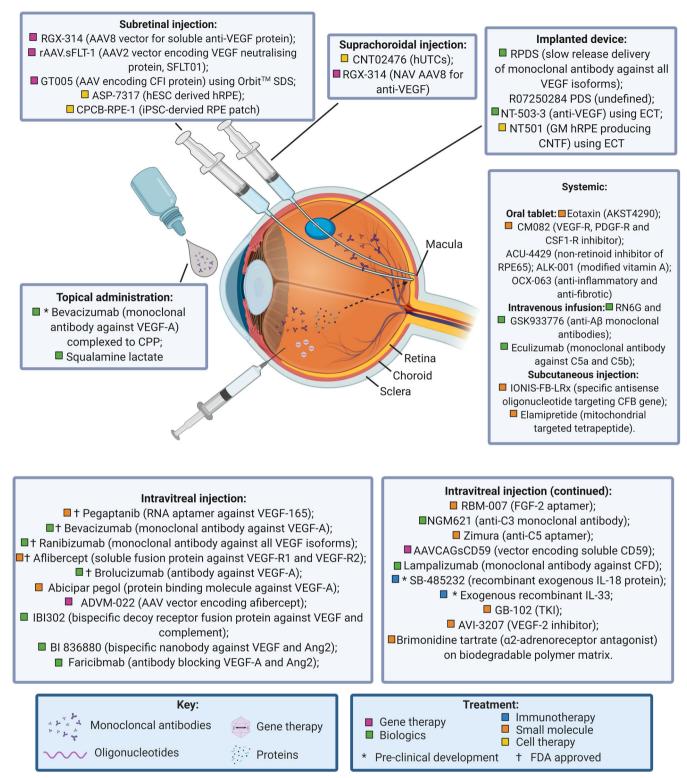
2.6 | Cell therapies

There is a loss of functional RPE and photoreceptors in GA, which are not endogenously replaced and can result in complete sight loss. Cell therapy offers a viable opportunity to replace these RPE cells, which are essential for the photoreceptor survival and function. Importantly, the replacement cells must integrate into the neural retina and provide functional as well as anatomical effects. Stem cells which are differentiated into RPE cells are very effective but are likely to be very expensive and might not be accessible for the millions of AMD patients experiencing vision loss. Immunosuppressive medicines are often taken to prevent rejection and another potential limitation of cell therapy is uncontrolled cell multiplication which can lead to tumour growth.
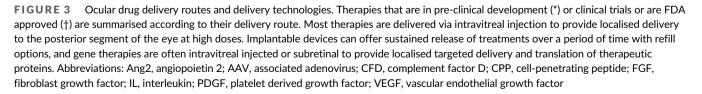
There are multiple cell therapies for dry AMD which have good safety results and have entered Phase II trials. ASP-7317 is therapy consisting of human RPE derived from human embryonic stem cells (hESC) administered by subretinal injection (Astellas Pharma Inc.,

Astellas Institute for Regenerative Medicine; NCT03178149), with primary completion date expected in 2027. Cells can also be grown on membranes, such as the CRCB-RPE1 (California Project to Cure Blindness RPE1) where ~100,000 hESC-derived human RPE are grown on a synthetic parylene membrane which replicates Bruch's membrane, to be transplanted via subretinal injection in patients with advanced dry AMD. This treatment showed feasibility and safety in mini pigs (Koss et al., 2016) and Phase I/II trials (Regenerative Patch Technologies, LLC; NCT02590692) excitingly demonstrate successful hESC-hRPE and host photoreceptor integration and some improved visual function in the short-term (12 months) (da Cruz et al., 2018; Kashani et al., 2018). OpRegen® is another cell-based therapy of hESC-derived hRPE and have showed long-term engraftment of the RPE and continued progressive functional improvement, with 6 out of 7 patients treated with OpRegen® showing improved BCVA up to 12 months (Therapeutics LC, 2020). The therapy was delivered either via the pars planar vitrectomy or using Orbit™ SDS (Gyroscope Therapeutics Limited), which allows a microinjection into the subretinal space without damaging the eye or a need for a vitrectomy or retinotomy. The Orbit™ SDS has recently received FDA 510(k) clearance (August 2020).

Induced-pluripotent derived stem cells (iPSCs) differentiated into RPE and grown on a biodegradable poly lactic-co-glycolic acid (PLGA) scaffold showed promising results in rodent and pig models (Sharma et al., 2019) and are in Phase I/IIa trials [National Eye Institute (NEI); NCT04339764] with 12 patients with advanced GA and will be monitored for 1 year. This therapy uses the patient's autologous blood cells to avoid transplant rejection. In 2015, RIKEN suspended the first clinical trials to use autologous iPSC transplants after treating a single patient with AMD (Garber, 2015), in spite of successful pre-clinical experiments (Kamao et al., 2014; Mandai, Fujii, et al., 2017) and an intact transplanted iPSC-derived RPE cell sheet under the retina at 1 year after surgery and no alterations in BCVA in Phase I trial in a patient with nAMD (UMIN-CTR number: UMIN000011929) (Mandai, Watanabe, et al., 2017).

A further cell therapy used human umbilical tissue-derived cells (hUTCs), which are not classed as a stem cell under the NIH definition as they do not grow indefinitely and do not spontaneously differentiate when transplanted into other cell types. hUTCs can also secrete neurotrophic factors which improve RPE function (Lund et al., 2007). Subretinal delivery of these hUTCs, called palucorcel (CNTO-2476) in Phase I/IIa trials (Janssen Research & Development, LLC; NCT01226628) induced a high rate of retinal perforations (13 patients) and retinal detachments (6 patients), out of 33 patients. Although there was localisation of palucorcel in the subretinal space and some improvement in visual acuity, the surgical approach must be modified to prevent adverse effects (Ho et al., 2017). In Phase IIb trials, a novel delivery system was used to deliver into the suprachoroidal space, which was mostly well tolerated, with 16/21 patients experiencing mild adverse effects which resolved within 1 month and no major adverse effects (retinal detachment and perforation), although there was no apparent effect of treatment observed with BCVA or GA area (Heier et al., 2020). Phase II trials were

FIGURE 3 Ocular drug delivery routes and delivery technologies. Therapies that are in pre-clinical development (*) or clinical trials or are FDA approved (†) are summarised according to their delivery route. Most therapies are delivered via intravitreal injection to provide localised delivery to the posterior segment of the eye at high doses. Implantable devices can offer sustained release of treatments over a period of time with refill options, and gene therapies are often intravitreal injected or subretinal to provide localised targeted delivery and translation of therapeutic proteins. Abbreviations: Ang2, angiopoietin 2; AAV, associated adenovirus; CFD, complement factor D; CPP, cell-penetrating peptide; FGF, fibroblast growth factor; IL, interleukin; PDGF, platelet derived growth factor; VEGF, vascular endothelial growth factor
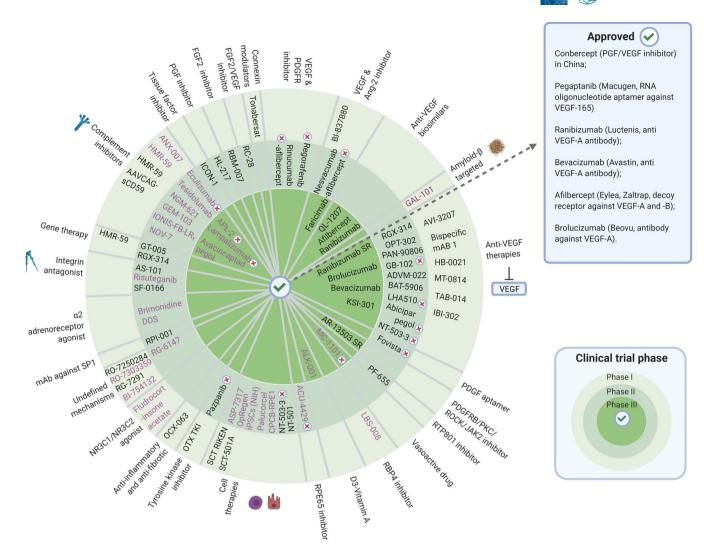
FIGURE 4 Emerging therapies in clinical trials for dry and nAMD. Phase I, II and III clinical trials for nAMD (black text) and dry AMD (purple text) are displayed in a wheel with type of treatment displayed. Clinical trials which were terminated or failed are indicated by a red cross. Approved trials in clinic are also displayed

withdrawn by company business decision (Janssen Pharmaceutical K.K. NCT02895815).

2.7 | Other therapies

There are other therapies in clinical trials for AMD which will be briefly mentioned. Clinical trials for dry AMD include ALK-001 (modified form of vitamin A D3) which is in Phase III trials as oral capsules (Alkeus Pharmaceuticals, Inc. SAGA study, NCT03845582); retinal binding protein 4 (RBP4) inhibitor LBS-008 (RBP4 Pty Ltd; NCT03735810); and subcutaneously delivery of a mitochondrial-targeted tetrapeptide which aims to reduce reactive oxygen species (ROS) (elamipretide, Stealth BioTherapeutics Inc. ReCLAIM-2 study; NCT03891875). Brimonidine tartrate (selective α_2-adrenoreceptor agonist) which is a commonly used glaucoma drug delivered via

intravitreal injection in a biodegradable polymer matrix is in early phase trials for dry AMD. Emixustat hydrochloride (ACU-4429) is an oral non-retinoid which inhibits RPE65, but has recently shown in Phase II/III trials no significant reduction in growth of GA compared to placebo over 2 years (Dugel et al., 2015; Rosenfeld, Dugel, et al., 2018). Tonabersat (SB-220453; OcuNexus Therapeutics) is a connexin-42 hemichannel blocker which is in early phase trials for dry and nAMD (Mat Nor et al., 2020). RG-6147 (Genentech, Inc. GALLEGO study, NCT03972709) and RG-7921 (Genentech, Inc.) are in early phase trials for GA but have undefined mechanisms of action. Topically administered MC-1101 is a vasoactive drug which increases choroidal blood flow and has some anti-inflammatory and anti-oxidant effects and is in Phase III trials for mild to moderate non-exudative (dry) AMD (MacuCLEAR, Inc. NCT02127463).

Early phase therapies for nAMD include an anti-inflammatory and anti-fibrotic therapy oral capsule OCX-063 (ANZCTR

TABLE 1 A selection of clinical trials of emerging therapies for AMD.

Compound (company)	Type of therapy	Disease	Delivery method, dose and dosing regime	Results [primary outcome measured for expected results]	Trial status and outcome	Trial number	References
AAV2-sFLT01 (Genzyme, Sanofi Company)	Gene therapy - AAV2 vector expressing the VEGF neutralising protein SFLT01	nAMD	Single intravitreal injection of 2×10^8, 2×10^9, 6×10^9, 2×10^{10} vector genomes.	Some temporary systemic effects, but generally safe and well tolerated.	Phase I completed July 2018	NCT01024998	Heier et al. (2017)
AAVCAGsCD59 (HMR59) (Hemera Biosciences)	Gene therapy - viral vector for soluble CD59, which will inhibit MAC formation (complement mediated cell lysis).	Dry AMD	Anti-VEGF at baseline then single intravitreal injection of AAVCAGsCD59 at 7 days of low, mid and high doses.	No results reported. [assessment of the number of anti-VEGF intravitreal injections required up to 12 months]	Phase I completed December 2019; Phase I estimated completion January 2022	NCT03144999 NCT03585556	
Abicipar pegol (AGN-150998, MP0112 (Allergan plc/Molecular partners)	Long-acting potent antagonist of VEGF-A with lower molecular weight, higher affinity and longer ocular half-life than ranibizumab.	Advanced nAMD	Abicipar pegol (2 mg) injected Day 1, Week 4 and Week 12, then every 12 weeks until Week 96, compared to ranibizumab (0.5 mg) intravitreal injections every 4 weeks.	Abicipar showed comparable BCVA and CRT up to 52 weeks with fewer injections than ranibizumab (last injection 12 vs 4 weeks). No serious adverse effects reported. Failed to gain FDA approval in 2020 due to significant intraocular inflammation (8.9% to 15.4%) and unfavourable risk–benefit ratio.	Phase I/II completed November 2010; Phase II (REACH trial) completed April 2014; Phase II completed December 2015; Phase III completed June 2019; Phase III (CEDAR trial) completed June 2019.	NCT01086761 NCT01397409 NCT02181504 NCT02462486 NCT02462928	Callanan et al. (2018); Khurana et al. (2020); Kunimoto et al. (2020); Souied et al. (2014)
ADVM-022 (Adverum Biotechnologies, Inc.)	ADVM-022 AAV. 7 m8-aflibercept, gene therapy to provide continuous delivery of aflibercept.	nAMD	Gene therapy, single intravitreal injection	Interim results: Long-term durability of >1 year from a single intravitreal injection with no rescue injections required in the higher dose 6×10^{11} vector genomes, but greatest improvements from 2×10^{11} vector genomes group (n = 9) with mean CRT change from baseline of	Phase I (OPTIC trial) expected June 2022.	NCT03748784	Khanani, Kiss, et al. (2020)

TABLE 1 (Continued)

Compound (company)	Type of therapy	Disease	Delivery method, dose and dosing regime	Results [primary outcome measured for expected results]	Trial status and outcome	Trial number	References
				−137.8 mm and mean BCVA gain from baseline of +6.8 letters at 20 weeks [type, severity, and incidence of ocular and systemic adverse events at 104 weeks]			
Aflibercept (Regeneron Pharmaceuticals and Bayer)	Recombinant soluble decoy receptor binds to VEGF-A and VEGF-B	nAMD	High dose intravitreal injections	No results reported. [assessing whether high dose provides greater intraocular pharmacodynamic effect and/or longer duration of action compared to intravitreal aflibercept injection]	Phase II (CANDELA) expected November 2021	NCT04126317	
AKST4290 (Alkahest, Inc.)	Antagonist at CCR3 (receptor for eotaxin)	nAMD	Efficacy of oral AKST4290 (400–800 mg twice daily for 36 weeks. Initial loading doses of aflibercept by intravitreal injection.	No results reported. [mean change from baseline in BCVA at 40 weeks]	Phase II (PHTHALO-205) expected April 2021	NCT04331730	
BAT5906 (Bio-Thera Solutions)	Recombinant anti-VEGF humanised monoclonal antibody.	nAMD	Single injection dose escalation from 0.3 mg	No results reported [evaluate safety and pharmacokinetics with dose escalation and immunogenicity profile].	Phase I expected June 2020	NCT04151212	
BI 836880 (Boehringer Ingelheim	A humanised bispecific nanobody that targets VEGF and Ang2.	nAMD	Single intravitreal injection followed by multiple intravitreal injections of several doses	No results reported [number of ocular doses limiting events and drug related adverse events].	Phase I expected October 2021	NCT03861234	
Brolucizumab/Beovu® (ESBA1008; RTH258) (Alcon Research)	Monoclonal antibody inhibits VEGF-A (smaller size and is delivered at a higher	nAMD	Intravitreal injection of brolucizumab (6 mg) administered three times at 4-week intervals with 84 days	Brolucizumab has similar adverse event risks with minimal systemic accumulation, therefore, is safe and	Phase I/II completed March 2013; Phase II completed August 2014; Phase II completed September	NCT01304693 NCT01796964 NCT02507388 NCT02434328 NCT02307682	Dugel et al. (2017, 2020); Dugel, Singh, et al. (2021)

(Continues)

TABLE 1 (Continued)

Compound (company)	Type of therapy	Disease	Delivery method, dose and dosing regime	Results [primary outcome measured for expected results]	Trial status and outcome	Trial number	References
	concentration than current anti-VEGF.		follow up compared to aflibercept (2 mg).	tolerable. Brolucizumab was non-inferior to aflibercept over 56 weeks, with more stable central subfield thickness reductions, fewer unscheduled treatments and higher rates of fluid resolution. FDA approved in 2019	2016; Phase III (HARRIER) completed March 2018; Phase III (HAWK) completed March 2018; Phase III (TALON) expected October 2022; Phase IV (ROBIN, Vista Klinik and Novartis) expected July 2021	NCT04287348 NCT04005352	
CM082 (also called X-82) (AnewPharma)	Oral multi kinase inhibitor that targets VEGFR, PDGFR and CSF1R.	nAMD	Oral tablet twice (25–50 mg) daily for 2 weeks followed by 2 weeks off in 4-week cycles. The treatment period is tentatively set at 1 year.	No results reported [dose-limiting toxicity]	Phase II expected January 2022	NCT03710863	
Faricimab (RO6867461; RG7716) (Hoffmann-La Roche)	Simultaneous blockade of Ang-2 and VEGF-A with the bispecific antibody via both simultaneous and independent binding.	nAMD	4 monthly intravitreal injections of faricimab (6.0 mg) then every 12 or 16 weeks, compared to 0.5 mg ranibizumab monthly.	Faricimab maintained initial vision and anatomical improvements compared to monthly ranibizumab, at Week 52.	Phase II (STAIRWAY) completed March 2018	NCT03038880	Khanani, Patel, et al. (2020)
GSK933776 (GlaxoSmithKline)	A humanised monoclonal antibody directed against the N-terminal amino acids of Aβ.	GA secondary to AMD	3, 6 or 15 mg/kg administration of GSK933776 via intravenous infusion	Intravenous Aβ inhibition with GSK933776 did not slow the rate of GA enlargement compared with placebo, and no clinically meaningful differences relative to placebo were observed in visual function testing over 18 months.	Phase II completed April 2016	NCT01342926	Rosenfeld, Berger, et al. (2018)
GT005 (Gyroscope Therapeutics)	A recombinant non-replicating adeno-			No safety concerns to date.	Phase I/II expected June 2021; Phase II	NCT03846193 NCT04437368	Ellis et al. (2020)

TABLE 1 (Continued)

Compound (company)	Type of therapy	Disease	Delivery method, dose and dosing regime	Results [primary outcome measured for expected results]	Trial status and outcome	Trial number	References
	associated viral (AAV) vector encoding a human complement factor I.	GA secondary to AMD	Single subretinal injection, testing 3 doses		(EXPLORE trial) expected February 2023		
IB1302 (Innovent Biologics, Suzou Co. Ltd.)	Novel bispecific decoy receptor fusion protein designed with domains to inhibit both VEGF and the complement cascade and are connected by the fc region of human immunoglobulin	nAMD	Dose escalation study to evaluate the safety and tolerability of a multiple dose intravitreal injection of IBI302 every 4 weeks (3 injections) followed by PRN dosing.	No results reported [BCVA, slit lamp examination, ophthalmoscopy, IOP, fundus photography and incidence of adverse events at Day 140]	Phase I expected June 2021	NCT04370379	Ren et al. (2016)
ICON-1 (hI-con1) (Ionic Therapeutics)	Factor VII-IgGFc chimeric protein targeting tissue factor. Anti-tissue factor immunoconjugate protein, binds to pathological vessels overexpressing tissue factor.	nAMD	Monthly intravitreal hI-con1 (0.3 mg) for the first 2 months followed by monthly treatment for 3 months or in combination with intravitreal ranibizumab (0.5 mg). Compared to monthly intravitreal injections of ranibizumab. Intravitreal injection of ICON-1 (0.6 mg) or ICON-1 (0.6 mg) combination therapy after initial afilbercept treatment (2 mg) or ICON-1 (0.6 mg) combination therapy with afilbercept treatment (2 mg).	HI-con1 in combination with ranibizumab demonstrates no adverse effects and some improvement in central retinal subfield thickness at 6 months	Phase II completed September 2016; Phase II (DECO trial) completed in April 2019	NCT02358889	NCT03452527
IONIS-FB-LRx (ISIS 696844; Ionis Pharmaceuticals, Inc.)	A novel specific antisense oligonucleotide (ASO) targeting the human CFB gene could reduce circulating	GA secondary to dry AMD	Ascending doses multiple subcutaneously every 4 weeks	A 72% reduction in plasma CFB levels at Day 36 and no safety or clinically relevant changes in blood chemistry,	Phase II (GOLDEN STUDY) expected October 2022	NCT03815825	Jaffe, Sahni, et al. (2020)

TABLE 1 (Continued)

Compound (company)	Type of therapy	Disease	Delivery method, dose and dosing regime	Results [primary outcome measured for expected results]	Trial status and outcome	Trial number	References
	levels of complement factor B (FB)			haematology, urinalysis, ECGs or vital signs. Phase 2 trials assess GA area growth rate over 12 months.			
Lampalizumab/ FCFD4514S (Genentech Inc., Hoffmann-La Roche)	Antigen-binding fragment of a humanised monoclonal antibody that inhibits complement factor D	GA secondary to AMD	10 mg by intravitreal injections every 4 or 6 weeks.	Phase 3 trials showed no meaningful differences in geographic atrophy lesion area at Week 48. Endophthalmitis in 5/12,447 injections (0.04%) or 5/1252 treated patients (0.4%) at Week 48.	Phase I completed July 2010; Phase II terminated February 2018; Phase III (CHROMA and SPECTRI trials) terminated January 2018.	NCT02247479 NCT02247531 NCT00973011 NCT01602120 NCT01229215 NCT02288559 NCT02247479 NCT02247531	Holz et al. (2018)
NGM621 (NGM Biopharmaceuticals, Inc.)	Humanised IgG1 monoclonal antibody engineered to potently inhibit complement C3	GA secondary to AMD	Single intravitreal injection every 4 or 8 weeks	No results reported [change of GA lesion area measured by FAF incidence and severity of ocular and systemic adverse events at 48 weeks]	Phase II (CATALINA) expected April 2023	NCT04465955	
rAAV.sFlt-1 (Adverum Biotechnologies, Inc.)	AAV2 vector expressing the VEGF neutralising protein SFLT01	nAMD	Single subretinal injection of 1×10^{11} vector genomes of rAAV.sFlt-1.	No systemic safety signals or serious adverse effects. Twelve (57%) of patients in the rAAV. sFLT-1 group maintained, or improved vision compared to four (36%) in the control group.	Phase I/IIa completed August 2017	NCT01494805	Constable et al. (2016); Rakoczy et al. (2015)
Ranibizumab port delivery system (RPDS) RO7250284 (Genentech, Hoffmann-La Roche)	Implantable, reservoir based, refillable, slow-release delivery system for ranibizumab (antibody fragment against VEGF-A)	nAMD	Sustained release of PDS implant with ranibizumab 100 mg ml^{-1}, with refill exchanges of 100 mg ml^{-1} ranibizumab every 24 weeks.	Similar visual acuity outcomes compared to monthly intraocular injections of ranibizumab and has a median refill time of 15 months. More adverse events	Phase II (LADDER) completed March 2019; Phase III (ARCHWAY) expected April 2021; Phase III (PORTAL) expected September 2025	NCT02510794 NCT03677934 NCT04567303 NCT03683251	Campochiaro et al. (2019)

TABLE 1 (Continued)

Compound (company)	Type of therapy	Disease	Delivery method, dose and dosing regime	Results [primary outcome measured for expected results]	Trial status and outcome	Trial number	References
				associated with surgical implantation of the device compared to regular intravitreal injections, with 179 of patients (8.9%) with a RPDS implantation developed serious adverse events including vitreous haemorrhage.			
RBM-007 (Ribomic USA, Inc.)	Anti-FGF-2 aptamer inhibits angiogenesis and scar formation	nAMD	Four monthly intravitreal injections of RBM-007 alone or in combination with, and four monthly RBM-007 injections in combination with aflibercept dosed at every other month	No results reported [change BCVA from Week 16].	Phase II (TOFU trial) expected June 2021	NCT04200248	
RC28-E (RemeGen)	A chimeric decoy receptor trap fusion protein by dual block of VEGF and FGF-2	nAMD	Dose escalation study 0.5–2 mg intravitreal injections up to 48 weeks.	No results reported [change in BCVA at 12 and 48 weeks, incidence and severity of adverse effects].	Phase I expected June 2020; Phase I/II expected October 2020	NCT03777254 NCT04270669	
RGX-314 (Regenxbio Inc.)	NAV-AAV8 vector containing gene for monoclonal antibody fragment to neutralise VEGF.	nAMD	RGX-314 gene therapy delivered via one or two suprachoroidal space (SCS) injections	No results reported [change in BCVA at 40 weeks]	Phase II (AAVIATE trial) expected February 2022	NCT04514653	
RN6G, PF-04382923 (Pfizer)	Anti-Aβ monoclonal antibody against Aβ40 and Aβ42	GA secondary to AMD	Intravenous 30-min infusion dose ranging from 2.5 to 15 mg/kg	Safe and well tolerated in phase I. no effects on BCVA or contrast sensitivity were observed.	Phase I completed March 2013; Phase II terminated in April 2013 due to organisational decision	NCT01577381 NCT01003691	Berger et al. (2013)
Squalamine lactate (MSI-1256F) (Genaera Corporation)	Squalamine lactate inhibits angiogenesis induced by VEGF, PDGF or bFGF.	nAMD	Intravenous injection weekly for 4 weeks, then every 4 weeks for 104 weeks.	Biological effect, dose response and visual acuity benefit in phase II trials, but had rapid	Phase II terminated February 2007; Phase II terminated May 2007; Phase III terminated	NCT00139282 NCT00094120 NCT00089830	

(Continues)

TABLE 1 (Continued)

Compound (company)	Type of therapy	Disease	Delivery method, dose and dosing regime	Results [primary outcome measured for expected results]	Trial status and outcome	Trial number	References
				clearance and impractical delivery			
Squalamine lactate (Ohr Pharmaceutical Inc.)	Squalamine lactate inhibits angiogenesis induced by VEGF, PDGF or bFGF.	nAMD	Topical 0.2% Squalamine eye drop	Trend towards better visual acuity in patients receiving OHR-102 eyedrops at 36 weeks, particularly in a subgroup of patients had classic lesions and CNV less than 10 mm^2. This subgroup of patients was specifically recruited for phase III trials (MAKO trial; NCT02727881) which failed and showed no efficacy analysis.	Phase II completed in March 2015; Phase III (MAKO trial) failed to meet primary endpoint.	NCT01678963 NCT02727881	
Tesidolumab, LFG316, (Novartis Pharmaceuticals)	High affinity antibody which inhibits C5 cleavage	GA associated with AMD	Intravitreal injection of 5 mg every 4 weeks, or a single 10 mg intravitreal injection and assessed after 12 weeks.	LFG316 did not significantly reduce GA lesion growth compared to sham controls.	Phase II completed June 2015	NCT01527500	Novartis (2015)
Zimura™ (avacincaptad pegol) (Ophthotech, INVERIC bio Inc.)	Anti-complement factor 5	GA secondary to dry AMD	Monthly intravitreal injections of Zimura™ or sham for 18 months.	No results reported [change in GA measured by FAF over 12 months]	Completed phase II/III April 2020: Phase III expected June 2023	NCT02686658 NCT04435366	Jaffe, Westby, et al. (2021)

Note: Completed and ongoing clinical trials for nAMD, geographic atrophy (GA) secondary to AMD and early dry AMD. The trial status reported is the study completion date accessed 11 May 2020 from clinicaltrials.gov.

Abbreviations: AAV, associated adenoviral vector; BCVA, best-corrected visual acuity; CFB, complement factor B; CRT, central retinal thickness; FAF, fundus auto fluorescence; GA, geographic atrophy; GPCR, G-protein coupled receptor.

number: ACTRN12619001607167); a monoclonal antibody against sphingolipid 1 (SP1) (Resolute Pharma, NTC); PF-655, an siRNA against **mTOR** (Quark Pharmaceuticals, Pfizer; MONET study, NCT00713518); and AR-13503 SR which is a **Rho kinase** and protein kinase C inhibitor (Aerie Pharmaceuticals; NCT03835884). Integrins are also a therapeutic target for AMD, with risuteganib (an anti-integrin peptide) in Phase II trials for GA (Shaw et al., 2020) and SF-0166 molecule integrin $\alpha v \beta 3$ antagonist in Phase II trials as a topical solution for nAMD patients (SciFluor Life Sciences, Inc. NCT02914639).

Therapies in pre-clinical development and clinical trials and their delivery route are summarised in Figure 3. Phase I, II and III clinical trials for nAMD and dry AMD and treatments which are clinically approved are displayed in Figure 4. A selection of in clinical trials are summarised in Table 1.

3 | CLINICAL TRANSLATION

The ultimate goal for drug discovery is clinical translation and treating human disease. There are a range of therapeutic agents in development paired with delivery technologies to overcome the physical and biological barriers which hinder their delivery to the posterior segment of the eye. There are a few things to consider when designing experiments to test novel therapeutics and delivery agents. Firstly, the choice of animal model is important to ensure that the outcomes are representative of what would happen in human pathology. The pre-clinical animal models for AMD provide insight into translatability, physiological outputs and toxicity, but there are anatomical differences between human and rodent eyes which need to be addressed, particularly in respect to ocular drug delivery experiments. The rodent lens occupies a large portion of the eyeball and contains less vitreous compared to a human eye and this can produce differences in drug biodistribution. Also, rodents do not have a macula in the retina, which is the primary structure affected by macular degeneration. Secondly, many ocular drug delivery studies are performed in young animals due to cost, ease of experiments and feasibility. However, there are age-related changes in the structure and function of the eye, meaning that successful drug delivery in a young eye might not be replicated in an elderly eye. Thirdly, there are multiple models of the disease pathologies in AMD, but often these are limited to modelling specific aspects of the disease. For example, the most commonly used model for studying nAMD, the laser-induced CNV model, involves stimulating abnormal choroidal angiogenesis, but does not induce this pathology through the initial cause but rather through more severe induction of CNV, which is likely not to resemble the process occurring in human AMD. Furthermore, there is no good single model of dry AMD and current models replicate part of the disease pathogenesis such as reduced autophagy, high fat diet, $CFH^{+/-}$, $SOD1^{-/-}$. Recently, there has been a research movement towards using human tissue for studying pathogenesis and testing novel therapeutics, with the organ-on-a-chip technology and human iPSC-derived organoids at the forefront. These technologies offer a vital improvement in pre-clinical model design. Finally, the pathway to clinical translation is often extensive and it can take ~15 years for novel therapeutic agents or drug delivery technologies to reach the clinic. The repurposing of FDA-approved therapies and delivery technologies will have faster translation for human use than novel, complex, unapproved materials and should be given serious consideration.

In addition, the endpoints of clinical trials are often late stage pathology such as drusen and fluorescent angiography/CNV size. There are no good biomarkers for detecting early AMD pathology, which makes clinical translation and testing of new therapies challenging. Artificial intelligence (AI)-mediated detection of disease could be used to support efficient endpoint identification for clinical trials, hopefully sooner in the disease pathogenesis, which will shorten necessary clinical trial length and accelerate clinical translation. The ability to detect pathology earlier could allow for intervention and treatment before disease onset. Although studies are in their early stages, AI could be used to predict AMD development. A landmark study has developed algorithms to detect if and when the second healthy eye in AMD patients develops CNV pathology and requires therapeutic intervention with anti-VEGF injections to prevent sight loss (Yim et al., 2020). Other studies have detected AMD development through OCT scans and using convolutional neural network (Hwang et al., 2019) and through morphological changes in cones and rods (von der Emde et al., 2019). These exciting advances in detecting AMD pathology could revolutionise the translation of early AMD therapies into the clinic.

4 | CONCLUSIONS

There are many emerging therapeutic agents in pre-clinical development and clinical trials for AMD. These could provide a complementary therapy in combination with existing anti-VEGF therapies for nAMD patients and provide a less invasive delivery route or longer acting effect and thus reduce the number of intravitreal injections required. There is still an urgent need for treatments to prevent sight loss in non-neovascular AMD, with many promising treatments emerging. There are many age and disease-related changes that occur in the eye which may affect ocular drug delivery and must be considered when designing therapeutics and pre-clinical studies. Novel delivery technologies such as the sustained release using the PDS and ECT could provide the opportunity for prolonged therapeutic delivery and fewer hospital visits for regular intravitreal injections. Gene therapies could offer the promise of a lifelong continuous supply of therapeutics, but with the high cost and a high percentage of patients who receive long-term anti-VEGF therapies becoming non-responsive and developing GA, there should be caution surrounding long-term anti-VEGF gene therapy. Most therapies in early phase trials for dry AMD have targeted the complement cascade, but there has been a high failure rate due to lack of efficacy and after more than a decade of attempts, other targets need to be explored.

Cell-based therapies are emerging and many treatments have entered Phase II trials, however, the expense of these treatments may not be accessible for the wider population. Furthermore, immunotherapies are an exciting avenue and target early dysregulation of the immune response in AMD, offering earlier intervention and prevention of disease progression. There are many promising emerging therapies for AMD and advances in ocular drug delivery technologies, which can be combined to develop new treatments to preserve sight in our ageing population.

4.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in the IUPHAR/BPS Guide to Pharmacology (http://www.guidetopharmacology.org), and are permanently archived in the Concise Guide to Pharmacology 2019/20 (Alexander, Fabbro, et al., 2019; Alexander, Kelly, et al., 2019).

ORCID
Chloe N. Thomas https://orcid.org/0000-0002-6202-1347
Dawn A. Sim https://orcid.org/0000-0002-6363-7805
Wen Hwa Lee https://orcid.org/0000-0002-4098-5225
Nada Alfahad https://orcid.org/0000-0002-1920-1756
Andrew D. Dick https://orcid.org/0000-0002-0742-3159
Alastair K. Denniston https://orcid.org/0000-0001-7849-0087
Lisa J. Hill https://orcid.org/0000-0001-8431-7029

REFERENCES
Aiello, L. P., Avery, R. L., Arrigg, P. G., Keyt, B. A., Jampel, H. D., Shah, S. T., Pasquale, L. R., Thieme, H., Iwamoto, M. A., Park, J. E., Nguyen, H. V., Aiello, L. M., Ferrara, N., & King, G. L. (1994). Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. *The New England Journal of Medicine*, 331, 1480–1487. https://doi.org/10.1056/NEJM199412013312203

Akhtar-Schafer, I., Wang, L., Krohne, T. U., Xu, H., & Langmann, T. (2018). Modulation of three key innate immune pathways for the most common retinal degenerative diseases. *EMBO Molecular Medicine*, 10, 1–27. https://doi.org/10.15252/emmm.201708259

Alexander, S. P. H., Fabbro, D., Kelly, E., Mathie, A., Peters, J. A., Veale, E. L., Armstrong, J. F., Faccenda, E., Harding, S. D., Pawson, A. J., Sharman, J. L., Southan, C., Davies, J. A., & CGTP Collaborators. (2019). THE CONCISE GUIDE TO PHARMACOLOGY 2019/20: Catalytic receptors. *British Journal of Pharmacology*, 176 (Suppl 1), S247–S296.

Alexander, S. P. H., Kelly, E., Mathie, A., Peters, J. A., Veale, E. L., Armstrong, J. F., Faccenda, E., Harding, S. D., Pawson, A. J., Sharman, J. L., Southan, C., Buneman, O. P., Cidlowski, J. A.,

Christopoulos, A., Davenport, A. P., Fabbro, D., Spedding, M., Striessnig, J., Davies, J. A., & CGTP Collaborators. (2019). THE CONCISE GUIDE TO PHARMACOLOGY 2019/20: Other Protein Targets. *British Journal of Pharmacology*, 176, S1–S20. https://doi.org/10.1111/bph.14747

Alvarado, J., Murphy, C., Polansky, J., & Juster, R. (1981). Age-related changes in trabecular meshwork cellularity. *Investigative Ophthalmology & Visual Science*, 21, 714–727.

Anderson, D. H., Talaga, K. C., Rivest, A. J., Barron, E., Hageman, G. S., & Johnson, L. V. (2004). Characterization of beta amyloid assemblies in drusen: The deposits associated with aging and age-related macular degeneration. *Experimental Eye Research*, 78, 243–256.

Annamalai, B., Parsons, N., Belhaj, M., Brandon, C., Potts, J., & Rohrer, B. (2018). Encapsulated cell technology-based delivery of a complement inhibitor reduces choroidal neovascularization in a mouse model. *Translational Vision Science & Technology*, 7, 1–13. https://doi.org/10.1167/tvst.7.2.3

Augustine, J., Pavlou, S., Ali, I., Harkin, K., Ozaki, E., Campbell, M., Stitt, A. W., Xu, H., & Chen, M. (2019). IL-33 deficiency causes persistent inflammation and severe neurodegeneration in retinal detachment. *Journal of Neuroinflammation*, 16, 1–15. https://doi.org/10.1186/s12974-019-1625-y

Bascones-Martinez, A., Mattila, R., Gomez-Font, R., & Meurman, J. H. (2014). Immunomodulatory drugs: Oral and systemic adverse effects. *Medicina Oral, Patología Oral Y Cirugía Bucal*, 19, e24–e31.

Berger, B., Garzone, P., Gunderson, I., Fanning, P., Wong, G., Liao, K., Hua, S., & Lin, J. (2013). Phase I, masked, placebo-controlled, single and multiple ascending intravenous dose studies evaluating systemic and ocular safety, tolerability, and visual acuity effects of RN6G (PF-04382923) in subjects with dry, age-related macular degeneration (ARMD). *Investigative Ophthalmology*, 54, 4505.

Bhatt, P., Narvekar, P., Lalani, R., Chougule, M. B., Pathak, Y., & Sutariya, V. (2019). An in vitro assessment of thermo-reversible gel formulation containing sunitinib nanoparticles for neovascular age-related macular degeneration. *AAPS PharmSciTech*, 20, 281. https://doi.org/10.1208/s12249-019-1474-0

Bird, A. C. (1992). Bruch's membrane change with age. *The British Journal of Ophthalmology*, 76, 166–168.

Bora, N. S., Kaliappan, S., Jha, P., Xu, Q., Sivasankar, B., Harris, C. L., Morgan, B. P., & Bora, P. S. (2007). CD59, a complement regulatory protein, controls choroidal neovascularization in a mouse model of wet-type age-related macular degeneration. *Journal of Immunology*, 178, 1783–1790.

Bora, N. S., Kaliappan, S., Jha, P., Xu, Q., Sohn, J. H., Dhaulakhandi, D. B., Kaplan, H. J., & Bora, P. S. (2006). Complement activation via alternative pathway is critical in the development of laser-induced choroidal neovascularization: Role of factor B and factor H. *Journal of Immunology*, 177, 1872–1878. https://doi.org/10.4049/jimmunol.177.3.1872

Bora, P. S., Sohn, J. H., Cruz, J. M., Jha, P., Nishihori, H., Wang, Y., Kaliappan, S., Kaplan, H. J., & Bora, N. S. (2005). Role of complement and complement membrane attack complex in laser-induced choroidal neovascularization. *Journal of Immunology*, 174, 491–497.

Callanan, D., Kunimoto, D., Maturi, R. K., Patel, S. S., Staurenghi, G., Wolf, S., Cheetham, J. K., Hohman, T. C., Kim, K., López, F. J., Schneider, S., & for the REACH Study Group. (2018). Double-masked, randomized, Phase 2 evaluation of abicipar pegol (an anti-VEGF DARPin therapeutic) in neovascular age-related macular degeneration. *Journal of Ocular Pharmacology and Therapeutics*, 34, 700–709. https://doi.org/10.1089/jop.2018.0062

Campochiaro, P. A., Marcus, D. M., Awh, C. C., Regillo, C., Adamis, A. P., Bantseev, V., Chiang, Y., Ehrlich, J. S., Erickson, S., Hanley, W. D.,

Horvath, J., Maass, K. F., Singh, N., Tang, F., & Bartesélli, G. (2019). The port delivery system with ranibizumab for neovascular age-related macular degeneration: Results from the randomized Phase 2 ladder clinical trial. *Ophthalmology*, *126*(8), 1141–1154. https://doi.org/10.1016/j.ophtha.2019.03.036

Campochiaro, P. A., Channa, R., Berger, B. B., Heier, J. S., Brown, D. M., Fiedler, U., Hepp, J., & Stumpp, M. T. (2013). Treatment of diabetic macular edema with a designed ankyrin repeat protein that binds vascular endothelial growth factor: A phase I/II study. *American Journal of Ophthalmology*, *155*, 697–704.704 e691–692

Campochiaro, P. A., Marcus, D. M., Awh, C. C., Regillo, C., Adamis, A. P., Bantseev, V., Chiang, Y., Ehrlich, J. S., Erickson, S., Hanley, W. D., Horvath, J., Maass, K. F., Singh, N., Tang, F., & Bartesell, G. (2019). The port delivery system with ranibizumab for neovascular age-related macular degeneration: Results from the randomized Phase 2 ladder clinical trial. *Ophthalmology*, *126*, 1141–1154.

Canna, S. W., Shi, G., Gery, I., & Sen, H. N. (2017). Chronic, systemic interleukin-18 does not promote macular degeneration or choroidal neovascularization. *Investigative Ophthalmology & Visual Science*, *58*, 1764–1765. https://doi.org/10.1167/iovs.17-21697

Cao, L., Wang, H., & Wang, F. (2013). Amyloid-beta-induced matrix metalloproteinase-9 secretion is associated with retinal pigment epithelial barrier disruption. *International Journal of Molecular Medicine*, *31*, 1105–1112. https://doi.org/10.3892/ijmm.2013.1310

Cashman, S. M., Ramo, K., & Kumar-Singh, R. (2011). A non membrane-targeted human soluble CD59 attenuates choroidal neovascularization in a model of age related macular degeneration. *PLoS One*, *6*, e19078. https://doi.org/10.1371/journal.pone.0019078

Ciulla, T. A., Criswell, M. H., Danis, R. P., Williams, J. I., McLane, M. P., & Holroyd, K. J. (2003). Squalamine lactate reduces choroidal neovascularization in a laser-injury model in the rat. *Retina*, *23*, 808–814.

Clare, A. J., Copland, D. A., Nicholson, L. B., Liu, J., Neal, C. R., Moss, S., Dick, A. D., & Theodoropoulou, S. (2020). Treatment with interleukin-33 is non-toxic and protects retinal pigment epithelium in an ageing model of outer retinal degeneration. *Journal of Cellular and Molecular Medicine*, *24*, 13546–13550.

Coffey, P. J., Gias, C., McDermott, C. J., Lundh, P., Pickering, M. C., Sethi, C., Bird, A., Fitzke, F. W., Maass, A., Chen, L. L., Holder, G. E., Luthert, P. J., Salt, T. E., Moss, S. E., & Greenwood, J. (2007). Complement factor H deficiency in aged mice causes retinal abnormalities and visual dysfunction. *Proceedings of the National Academy of Sciences of the United States of America*, *104*, 16651–16656.

Constable, I. J., Pierce, C. M., Lai, C. M., Magno, A. L., Degli-Esposti, M. A., French, M. A., McAllister, I. L., Butler, S., Barone, S. B., Schwartz, S. D., Blumenkranz, M. S., & Rakoczy, E. P. (2016). Phase 2a randomized clinical trial: Safety and post hoc analysis of subretinal rAAV.sFLT-1 for wet age-related macular degeneration. *eBioMedicine*, *14*, 168–175. https://doi.org/10.1016/j.ebiom.2016.11.016

Copland, D. A., Theodoropoulou, S., Liu, J., & Dick, A. D. (2018). A perspective of AMD through the eyes of immunology. *Investigative Ophthalmology & Visual Science*, *59*, AMD83–AMD92. https://doi.org/10.1167/iovs.18-23893

Csaky, K. G., Dugel, P. U., Pierce, A. J., Fries, M. A., Kelly, D. S., Danis, R. P., Wurzelmann, J. I., Xu, C.-F., Hossain, M., & Trivedi, T. (2015). Clinical evaluation of pazopanib eye drops versus ranibizumab intravitreal injections in subjects with neovascular age-related macular degeneration. *Ophthalmology*, *122*, 579–588. https://doi.org/10.1016/j.ophtha.2014.09.036

da Cruz, L., Fynes, K., Georgiadis, O., Kerby, J., Luo, Y. H., Ahmado, A., Vernon, A., Daniels, J. T., Nommiste, B., Hasan, S. M., Gooljar, S. B., Carr, A.-J. F., Vugler, A., Ramsden, C. M., Bictash, M., Fenster, M., Steer, J., Harbinson, T., Wilbrey, A., … Coffey, P. J. (2018). Phase 1 clinical study of an embryonic stem cell-derived retinal pigment epithelium patch in age-related macular degeneration. *Nature Biotechnology*, *36*, 328–337.

Danis, R., McLaughlin, M. M., Tolentino, M., Staurenghi, G., Ye, L., Xu, C.-F., Kim, R. Y., Johnson, M. W., & Pazopanib Eye Drops Study Group. (2014). Pazopanib eye drops: A randomised trial in neovascular age-related macular degeneration. *The British Journal of Ophthalmology*, *98*, 172–178. https://doi.org/10.1136/bjophthalmol-2013-303117

de Cogan, F., Hill, L. J., Lynch, A., Morgan-Warren, P. J., Lechner, J., Berwick, M. R., Peacock, A. F. A., Chen, M., Scott, R. A. H., Xu, H., & Logan, A. (2017). Topical delivery of anti-VEGF drugs to the ocular posterior segment using cell-penetrating peptides. *Investigative Ophthalmology & Visual Science*, *58*, 2578–2590. https://doi.org/10.1167/iovs.16-20072

Del Amo, E. M., Rimpela, A. K., Heikkinen, E., Kari, O. K., Ramsay, E., Lajunen, T., Schmitt, M., Pelkonen, L., Bhattacharya, M., Richardson, D., Subrizi, A., Turunen, T., Reinisalo, M., Itkonen, J., Toropainen, E., Casteleijn, M., Kidron, H., Antopolsky, M., Vellonen, K.-S., … Urtti, A. (2017). Pharmacokinetic aspects of retinal drug delivery. *Progress in Retinal and Eye Research*, *57*, 134–185. https://doi.org/10.1016/j.preteyeres.2016.12.001

Di Zazzo, A., Micera, A., Coassin, M., Varacalli, G., Foulsham, W., De Piano, M., & Bonini, S. (2019). InflammAging at ocular surface: Clinical and biomolecular analyses in healthy volunteers. *Investigative Ophthalmology & Visual Science*, *60*, 1769–1775. https://doi.org/10.1167/iovs.18-25822

Diestelhorst, M., & Kriegistein, G. K. (1992). Does aqueous humor secretion decrease with age? *International Ophthalmology*, *16*, 305–309. https://doi.org/10.1007/BF00917981

Ding, J. D., Johnson, L. V., Herrmann, R., Farsiu, S., Smith, S. G., Groelle, M., Mace, B. E., Sullivan, P., Jamison, J. A., Kelly, U., Harrabi, O., Bollini, S. S., Dilley, J., Kobayashi, D., Kuang, B., Li, W., Pons, J., Lin, J. C., & Rickman, C. B. (2011). Anti-amyloid therapy protects against retinal pigmented epithelium damage and vision loss in a model of age-related macular degeneration. *Proceedings of the National Academy of Sciences of the United States of America*, *108*, E279–E287. https://doi.org/10.1073/pnas.1100901108

Ding, J. D., Lin, J., Mace, B. E., Herrmann, R., Sullivan, P., & Bowes, R. C. (2008). Targeting age-related macular degeneration with Alzheimer's disease based immunotherapies: Anti-amyloid-beta antibody attenuates pathologies in an age-related macular degeneration mouse model. *Vision Research*, *48*, 339–345.

Doyle, S. L., Campbell, M., Ozaki, E., et al. (2012). NLRP3 has a protective role in age-related macular degeneration through the induction of IL-18 by drusen components. *Nature Medicine*, *18*, 791–798. https://doi.org/10.1038/nm.2717

Doyle, S. L., Lopez, F. J., Celkova, L., Brennan, K., Mulfaul, K., Ozaki, E., Kenna, P. F., Kurali, E., Hudson, N., Doggett, T., Ferguson, T. A., Humphries, P., Adamson, P., & Campbell, M. (2015). IL-18 immunotherapy for neovascular AMD: Tolerability and efficacy in nonhuman primates. *Investigative Ophthalmology & Visual Science*, *56*, 5424–5430. https://doi.org/10.1167/iovs.15-17264

Doyle, S. L., Lopez, F. J., Humphries, P., Adamson, P., & Campbell, M. (2015). Author response: The role of IL-18 in the treatment of AMD. *Investigative Ophthalmology & Visual Science*, *56*, 8237–8238.

Doyle, S. L., Ozaki, E., Brennan, K., Humphries, M. M., Mulfaul, K., Keaney, J., Kenna, P. F., Maminishkis, A., Kiang, A.-S., Saunders, S. P., Hams, E., Lavelle, E. C., Gardiner, C., Fallon, P. G., Adamson, P., Humphries, P., & Campbell, M. (2014). IL-18 attenuates experimental choroidal neovascularization as a potential therapy for wet age-related macular degeneration. *Science Translational Medicine*, *6*, 230ra244.

Dugel, P. U., Jaffe, G. J., Sallstig, P., Warburton, J., Weichselberger, A., Wieland, M., & Singerman, L. (2017). Brolucizumab versus aflibercept in participants with neovascular age-related macular degeneration: A randomized trial. *Ophthalmology*, *124*, 1296–1304. https://doi.org/10.1016/j.ophtha.2017.03.057

Dugel, P. U., Koh, A., Ogura, Y., Jaffe, G. J., Schmidt-Erfurth, U., Brown, D. M., Gomes, A. V., Warburton, J., Weichselberger, A., Holz, F. G., & HAWK and HARRIER Study Investigators. (2020). HAWK and HARRIER: Phase 3, multicenter, randomized, double-masked trials of brolucizumab for neovascular age-related macular degeneration. *Ophthalmology*, *127*, 72–84. https://doi.org/10.1016/j.ophtha.2019.04.017

Dugel, P. U., Novack, R. L., Csaky, K. G., Richmond, P. P., Birch, D. G., & Kubota, R. (2015). Phase II, randomized, placebo-controlled, 90-day study of emixustat hydrochloride in geographic atrophy associated with dry age-related macular degeneration. *Retina*, *35*, 1173–1183. https://doi.org/10.1097/IAE.0000000000000606

Dugel, P. U., Singh, R. P., Koh, A., Ogura, Y., Weissgerber, G., Gedif, K., Jaffe, G. J., Tadayoni, R., Schmidt-Erfurth, U., & Holz, F. G. (2021). HAWK and HARRIER: Ninety-six-week outcomes from the Phase 3 trials of brolucizumab for neovascular age-related macular degeneration. *Ophthalmology*, *128*(1), 89–99. https://doi.org/10.1016/j.ophtha.2020.06.028

Dunn, E. N., Hariprasad, S. M., & Sheth, V. S. (2017). An overview of the fovista and rinucumab trials and the fate of anti-PDGF medications. *Ophthalmic Surgery, Lasers & Imaging Retina*, *48*, 100–104.

Ellis, S., Buchberger, A., Holder, J., Orhan, E., & Hughes, J. (2020). GT005, a gene therapy for the treatment of dry age-related macular degeneration (AMD). *Investigative Ophthalmology*, *61*, 2295.

Falavarjani, K. G., & Nguyen, Q. D. (2013). Adverse events and complications associated with intravitreal injection of anti-VEGF agents: A review of literature. *Eye (London, England)*, *27*, 787–794.

Garber, K. (2015). RIKEN suspends first clinical trial involving induced pluripotent stem cells. *Nature Biotechnology*, *33*, 890–891. https://doi.org/10.1038/nbt0915-890

Gipson, I. K. (2013). Age-related changes and diseases of the ocular surface and cornea. *Investigative Opthalmology & Visual Science*, *54*(14), ORSF48–ORSF53. https://doi.org/10.1167/iovs.13-12840

Gonzales, C. R., & Group VISiONCT. (2005). Enhanced efficacy associated with early treatment of neovascular age-related macular degeneration with pegaptanib sodium: An exploratory analysis. *Retina*, *25*, 815–827. https://doi.org/10.1097/00006982-200510000-00001

Gonzalez-Chomon, C., Concheiro, A., & Alvarez-Lorenzo, C. (2011). Drug-eluting intraocular lenses. *Materials (Basel)*, *4*, 1927–1940.

Gragoudas, E. S., Adamis, A. P., Cunningham, E. T. Jr., Feinsod, M., & Guyer, D. R. (2004). Group VISiONCT. Pegaptanib for neovascular age-related macular degeneration. *The New England Journal of Medicine*, *351*, 2805–2816.

GraybugVision. (2019a). Graybug vision presents top line results of Phase 1/2a ADAGIO study at Hawaiian Eye & Retina 2019.

GraybugVision. (2019b). Graybug vision initiates Phase 2b (ALTISSIMO) Clinical Trial of GB-102 in patients with wet age-related macular degeneration.

Hageman, G. S., Anderson, D. H., Johnson, L. V., Hancox, L. S., Taiber, A. J., Hardisty, L. I., Hageman, J. L., Stockman, H. A., Borchardt, J. D., Gehrs, K. M., Smith, R. J. H., Silvestri, G., Russell, S. R., Klaver, C. C. W., Barbazetto, I., Chang, S., Yannuzzi, L. A., Barile, G. R., Merriam, J. C., … Allikmets, R. (2005). A common haplotype in the complement regulatory gene factor H (HF1/CFH) predisposes individuals to age-related macular degeneration. *Proceedings of the National Academy of Sciences of the United States of America*, *102*, 7227–7232. https://doi.org/10.1073/pnas.0501536102

Handa, J. T., Bowes Rickman, C., Dick, A. D., Gorin, M. B., Miller, J. W., Toth, C. A., Ueffing, M., Zarbin, M., & Farrer, L. A. (2019). A systems biology approach towards understanding and treating non-neovascular age-related macular degeneration. *Nature Communications*, *10*, 3347. https://doi.org/10.1038/s41467-019-11262-1

Heier, J. S., Ho, A. C., Samuel, M. A., Chang, T., Riemann, C. D., Kitchens, J. W., Slakter, J. S., Leiderman, Y. I., Spencer, R., Williams, G. A., Hickson-Curran, S. B., Keane, M., Baldassarre, J. S., & Prelude Study Group. (2020). Safety and efficacy of subretinally administered palucorcel for geographic atrophy of age-related macular degeneration: Phase 2b study. *Ophthalmology Retina*, *4*, 384–393. https://doi.org/10.1016/j.oret.2019.11.011

Heier, J. S., Kherani, S., Desai, S., Dugel, P., Kaushal, S., Cheng, S. H., Delacono, C., Purvis, A., Richards, S., le-Halpere, A., Connelly, J., Wadsworth, S. C., Varona, R., Buggage, R., Scaria, A., & Campochiaro, P. A. (2017). Intravitreous injection of AAV2-sFLT01 in patients with advanced neovascular age-related macular degeneration: A Phase 1, open-label trial. *Lancet*, *390*, 50–61. https://doi.org/10.1016/S0140-6736(17)30979-0

Heier, J. S., Wykoff, C. C., Waheed, N. K., Kitchens, J. W., Patel, S. S., Vitti, R., Perlee, L., Chu, K. W., Leal, S., Asmus, F., Son, V., Schmelter, T., & Brown, D. M. (2020). Intravitreal combined aflibercept + anti-platelet-derived growth factor receptor beta for neovascular age-related macular degeneration: Results of the Phase 2 CAPELLA trial. *Ophthalmology*, *127*, 211–220. https://doi.org/10.1016/j.ophtha.2019.09.021

Hermann, R. (2019). *GAL-101: Novel Phase 2 small molecule for neuroprotection and functional improvement in dry AMD and glaucoma*. San Fransisco: Ophthalmology Innovation Summit.

Hirano, Y., Yasuma, T., Mizutani, T., Fowler, B. J., Tarallo, V., Yasuma, R., Kim, Y., Bastos-Carvalho, A., Kerur, N., Gelfand, B. D., Bogdanovich, S., He, S., Zhang, X., Nozaki, M., Ijima, R., Kaneko, H., Ogura, Y., Terasaki, H., Nagai, H., … Ambati, J. (2014). IL-18 is not therapeutic for neovascular age-related macular degeneration. *Nature Medicine*, *20*, 1372–1375. https://doi.org/10.1038/nm.3671

Ho, A. C., Chang, T. S., Samuel, M., Williamson, P., Willenbucher, R. F., & Malone, T. (2017). Experience with a subretinal cell-based therapy in patients with geographic atrophy secondary to age-related macular degeneration. *American Journal of Ophthalmology*, *179*, 67–80.

Holash, J., Davis, S., Papadopoulos, N., Croll, S. D., Ho, L., Russell, M., Boland, P., Leidich, R., Hylton, D., Burova, E., Ioffe, E., Huang, T., Radziejewski, C., Bailey, K., Fandl, J. P., Daly, T., Wiegand, S. J., Yancopoulos, G. D., & Rudge, J. S. (2002). VEGF-trap: A VEGF blocker with potent antitumor effects. *Proceedings of the National Academy of Sciences of the United States of America*, *99*, 11393–11398. https://doi.org/10.1073/pnas.172398299

Holz, F. G., Dugel, P. U., Weissgerber, G., Hamilton, R., Silva, R., Bandello, F., Larsen, M., Weichselberger, A., Wenzel, A., Schmidt, A., Escher, D., Sararols, L., & Souied, E. (2016). Single-chain antibody fragment VEGF inhibitor RTH258 for neovascular age-related macular degeneration: A randomized controlled study. *Ophthalmology*, *123*, 1080–1089. https://doi.org/10.1016/j.ophtha.2015.12.030

Holz, F. G., Sadda, S. R., Busbee, B., Chew, E. Y., Mitchell, P., Tufail, A., Brittain, C., Ferrara, D., Gray, S., Honigberg, L., Martin, J., Tong, B., Ehrlich, J. S., Bressler, N. M., & for the Chroma and Spectri Study Investigators. (2018). Efficacy and safety of lampalizumab for geographic atrophy due to age-related macular degeneration Chroma and Spectri Phase 3 randomized clinical trials. *Jama Ophthalmology*, *136*, 666–677. https://doi.org/10.1001/jamaophthalmol.2018.1544

Hwang, D. K., Hsu, C. C., Chang, K. J., Chao, D., Sun, C. H., Jheng, Y. C., Yarmishyn, A. A., Wu, J. C., Tsai, C. Y., Wang, M. L., Peng, C. H., Chien, K. H., Kao, C. L., Lin, T. C., Woung, L. C., Chen, S. J., & Chiou, S. H. (2019). Artificial intelligence-based decision-making for age-related macular degeneration. *Theranostics*, *9*, 232–245. https://doi.org/10.7150/thno.28447

Ijima, R., Kaneko, H., Ye, F., Nagasaka, Y., Takayama, K., Kataoka, K., Kachi, S., Iwase, T., & Terasaki, H. (2014). Interleukin-18 induces retinal pigment epithelium degeneration in mice. *Investigative*

Ophthalmology & Visual Science, 55, 6673–6678. https://doi.org/10.1167/iovs.14-15367

Jaffe, G., Sahni, J., Fauser, S., Geary, R., Schneider, E., & McCaleb, M. (2020). Development of IONIS-FB-LRx to treat geographic atrophy associated with AMD. *Investigative Ophthalmology*, 61, 4305.

Jaffe, G. J., Ciulla, T. A., Ciardella, A. P., Devin, F., Dugel, P. U., Eandi, C. M., Masonson, H., Monés, J., Pearlman, J. A., Quaranta-El Maftouhi, M., & Ricci, F. (2017). Dual antagonism of PDGF and VEGF in neovascular age-related macular degeneration: A phase IIb, multicenter, randomized controlled trial. *Ophthalmology*, 124, 224–234. https://doi.org/10.1016/j.ophtha.2016.10.010

Jaffe, G. J., Eliott, D., Wells, J. A., Prenner, J. L., Papp, A., & Patel, S. (2016). A Phase 1 study of intravitreous E10030 in combination with ranibizumab in neovascular age-related macular degeneration. *Ophthalmology*, 123, 78–85.

Jaffe, G. J., Westby, K., Csaky, K. G., Monés, J., Pearlman, J. A., Patel, S. S., Joondeph, B. C., Randolph, J., Masonson, H., & Rezaei, K. A. (2021). C5 inhibitor avacincaptad pegol for geographic atrophy due to age-related macular degeneration: A randomized pivotal Phase 2/3 trial. *Ophthalmology*, 128(4), 576–586. https://doi.org/10.1016/j.ophtha.2020.08.027

Johnson, L. V., Leitner, W. P., Staples, M. K., & Anderson, D. H. (2001). Complement activation and inflammatory processes in drusen formation and age related macular degeneration. *Experimental Eye Research*, 73, 887–896.

Joussen, A. M., Wolf, S., Kaiser, P. K., Boyer, D., Schmelter, T., Sandbrink, R., Zeitz, O., Deeg, G., Richter, A., Zimmermann, T., Hoechel, J., Buetehorn, U., Schmitt, W., Stemper, B., & Boettger, M. K. (2019). The developing regorafenib eye drops for neovascular age-related macular degeneration (DREAM) study: An open-label phase II trial. *British Journal of Clinical Pharmacology*, 85, 347–355. https://doi.org/10.1111/bcp.13794

Kamao, H., Mandai, M., Okamoto, S., Sakai, N., Suga, A., Sugita, S., Kiryu, J., & Takahashi, M. (2014). Characterization of human induced pluripotent stem cell-derived retinal pigment epithelium cell sheets aiming for clinical application. *Stem Cell Reports*, 2, 205–218. https://doi.org/10.1016/j.stemcr.2013.12.007

Kashani, A. H., Lebkowski, J. S., Rahhal, F. M., Avery, R. L., Salehi-Had, H., Dang, W., Lin, C.-M., Mitra, D., Zhu, D., Thomas, B. B., Hikita, S. T., Pennington, B. O., Johnson, L. V., Clegg, D. O., Hinton, D. R., & Humayun, M. S. (2018). A bioengineered retinal pigment epithelial monolayer for advanced, dry age-related macular degeneration. *Science Translational Medicine*, 10, eaao4097.

Kauper, K., McGovern, C., Stabila, P., Sherman, S., Heatherton, P., Dean, B., Cortellessa, C., Lee, A., & Tao, W. (2013). Continuous intraocular drug delivery over 5 ½ years: Ciliary neurotrophic factor (CNTF) production by encapsulated cell technology implants treating patients with retinitis pigmentosa and geographic atrophy. *Investigative Ophthalmology & Visual Science*, 54, 3295.

Keck, P. J., Hauser, S. D., Krivi, G., Sanzo, K., Warren, T., Feder, J., & Connolly, D. (1989). Vascular permeability factor, an endothelial cell mitogen related to PDGF. *Science*, 246, 1309–1312. https://doi.org/10.1126/science.2479987

Khanani, A., Kiss, S., Turpcu, A., Hoang, C., & Osborne, A. (2020). Phase 1 study of intravitreal gene therapy ADVM-022 for neovascular AMD (OPTIC trial). *Investigative Ophthalmology*, 61, 1154.

Khanani, A. M., Patel, S. S., Ferrone, P. J., Osborne, A., Sahni, J., Grzeschik, S., Basu, K., Ehrlich, J. S., Haskova, Z., & Dugel, P. U. (2020). Efficacy of every four monthly and quarterly dosing of faricimab vs ranibizumab in neovascular age-related macular degeneration: The STAIRWAY Phase 2 randomized clinical trial. *JAMA Ophthalmol*, 138, 964–972. https://doi.org/10.1001/jamaophthalmol.2020.2699

Khurana, R. N., Kunimoto, D., Yoon, Y. H., Wykoff, C. C., Chang, A., Maturi, R. K., Agostini, H., Souied, E., Chow, D. R., Lotery, A. J., Ohji, M., Bandello, F., Belfort, R. Jr., Li, X. Y., Jiao, J., le, G., Kim, K., Schmidt, W., & Hashad, Y. (2020). Two-year results of the Phase 3 randomized controlled study of abicipar in neovascular age-related macular degeneration. *Ophthalmology*, 1–12. https://doi.org/10.1016/j.ophtha.2020.11.017

Kim, J., Kim, C. S., Jo, K., Cho, Y. S., Kim, H. G., Lee, G. H., Lee, Y. M., Sohn, E., & Kim, J. S. (2015). HL-217, a new topical anti-angiogenic agent, inhibits retinal vascular leakage and pathogenic subretinal neovascularization in Vldlr(−)/(−) mice. *Biochemical and Biophysical Research Communications*, 456, 53–58.

Kiss, S. (2016). *Key learnings from a Phase 2 study of encapsulated cell therapy for the treatment of neovascular AMD*. San Francisco: American Society of Retina Specialists annual meeting.

Koss, M. J., Falabella, P., Stefanini, F. R., Pfister, M., Thomas, B. B., Kashani, A. H., Brant, R., Zhu, D., Clegg, D. O., & Hinton, D. R. (2016). Subretinal implantation of a monolayer of human embryonic stem cell-derived retinal pigment epithelium: A feasibility and safety study in Yucatan minipigs. *Graefe's Archive for Clinical and Experimental Ophthalmology*, 254, 1553–1565.

Krohne, T. U., Liu, Z., Holz, F. G., & Meyer, C. H. (2012). Intraocular pharmacokinetics of ranibizumab following a single intravitreal injection in humans. *American Journal of Ophthalmology*, 154, 682–686.e682

Kunimoto, D., Yoon, Y. H., Wykoff, C. C., Chang, A., Khurana, R. N., Maturi, R. K., Agostini, H., Souied, E., Chow, D. R., Lotery, A. J., Ohji, M., Bandello, F., Belfort R Jr, Li, X. Y., Jiao, J., le, G., Schmidt, W., Hashad, Y., & CEDAR and SEQUOIA Study Groups. (2020). Efficacy and safety of abicipar in neovascular age-related macular degeneration: 52-week results of Phase 3 randomized controlled study. *Ophthalmology*, 127, 1331–1344. https://doi.org/10.1016/j.ophtha.2020.03.035

Lai, C. M., Estcourt, M. J., Wikstrom, M., Himbeck, R. P., Barnett, N. L., Brankov, M., Tee, L. B., Dunlop, S. A., Degli-Esposti, M. A., & Rakoczy, E. P. (2009). rAAV.sFlt-1 gene therapy achieves lasting reversal of retinal neovascularization in the absence of a strong immune response to the viral vector. *Investigative Ophthalmology & Visual Science*, 50, 4279–4287. https://doi.org/10.1167/iovs.08-3253

Lakkaraju, A., Toops, K. A., & Xu, J. (2014). Should I stay or should I go? Trafficking of sub-lytic MAC in the retinal pigment epithelium. *Advances in Experimental Medicine and Biology*, 801, 267–274. https://doi.org/10.1007/978-1-4614-3209-8_34

Lamkanfi, M., & Dixit, V. M. (2009). IL-33 raises alarm. *Immunity*, 31, 5–7.

Lee, K. S., Lin, S., Copland, D. A., Dick, A. D., & Liu, J. (2021). Cellular senescence in the aging retina and developments of senotherapies for age-related macular degeneration. *Journal of Neuroinflammation*, 18, 1–17. https://doi.org/10.1186/s12974-021-02088-0

Leung, D. W., Cachianes, G., Kuang, W. J., Goeddel, D. V., & Ferrara, N. (1989). Vascular endothelial growth factor is a secreted angiogenic mitogen. *Science*, 246, 1306–1309. https://doi.org/10.1126/science.2479986

Lewis, M. L., Davis, J., & Chuang, E. (1993). Interferon alfa-2a in the treatment of exudative age-related macular degeneration. *Graefe's Archive for Clinical and Experimental Ophthalmology*, 231, 615–618. https://doi.org/10.1007/BF00921954

Liew, F. Y., Girard, J. P., & Turnquist, H. R. (2016). Interleukin-33 in health and disease. *Nature Reviews. Immunology*, 16, 676–689.

Luckoff, A., Caramoy, A., Scholz, R., Prinz, M., Kalinke, U., & Langmann, T. (2016). Interferon-beta signaling in retinal mononuclear phagocytes attenuates pathological neovascularization. *EMBO Molecular Medicine*, 8, 670–678.

Lund, R. D., Wang, S., Lu, B., Girman, S., Holmes, T., Sauvé, Y., Messina, D. J., Harris, I. R., Kihm, A. J., Harmon, A. M., & Chin, F. Y. (2007). Cells isolated from umbilical cord tissue rescue photoreceptors and visual functions in a rodent model of retinal disease. *Stem Cells*, 25, 602–611.

Mains, J., & Wilson, C. G. (2013). The vitreous humor as a barrier to nanoparticle distribution. *Journal of Ocular Pharmacology and Therapeutics*, *29*, 143–150.

Mandai, M., Fujii, M., Hashiguchi, T., Sunagawa, G. A., Ito, S. I., Sun, J., Kaneko, J., Sho, J., Yamada, C., & Takahashi, M. (2017). iPSC-derived retina transplants improve vision in rd1 end-stage retinal-degeneration mice. *Stem Cell Reports*, *8*, 1112–1113. https://doi.org/10.1016/j.stemcr.2017.03.024

Mandai, M., Watanabe, A., Kurimoto, Y., Hirami, Y., Morinaga, C., Daimon, T., Fujihara, M., Akimaru, H., Sakai, N., Shibata, Y., & Terada, M. (2017). Autologous induced stem-cell-derived retinal cells for macular degeneration. *The New England Journal of Medicine*, *376*, 1038–1046. https://doi.org/10.1056/NEJMoa1608368

Marneros, A. G. (2013). NLRP3 inflammasome blockade inhibits VEGF-A-induced age-related macular degeneration. *Cell Reports*, *4*, 945–958.

Mat Nor, M. N., Rupenthal, I. D., Green, C. R., & Acosta, M. L. (2020). Connexin hemichannel block using orally delivered tonabersat improves outcomes in animal models of retinal disease. *Neurotherapeutics*, *17*, 371–387. https://doi.org/10.1007/s13311-019-00786-5

Matsuda, Y., Nonaka, Y., Futakawa, S., Imai, H., Akita, K., Nishihata, T., Fujiwara, M., Ali, Y., Bhisitkul, R. B., & Nakamura, Y. (2019). Anti-angiogenic and anti-scarring dual action of an anti-fibroblast growth factor 2 aptamer in animal models of retinal disease. *Molecular Therapy—Nucleic Acids*, *17*, 819–828. https://doi.org/10.1016/j.omtn.2019.07.018

Matsumura, N., Kamei, M., Tsujikawa, M., Suzuki, M., Xie, P., & Nishida, K. (2012). Low-dose lipopolysaccharide pretreatment suppresses choroidal neovascularization via IL-10 induction. *PLoS One*, *7*, e39890. https://doi.org/10.1371/journal.pone.0039890

Michels, S., Rosenfeld, P. J., Puliafito, C. A., Marcus, E. N., & Venkatraman, A. S. (2005). Systemic bevacizumab (Avastin) therapy for neovascular age-related macular degeneration twelve-week results of an uncontrolled open-label clinical study. *Ophthalmology*, *112*, 1035–1047.

Miller, J. W., Adamis, A. P., Shima, D. T., D'Amore, P. A., Moulton, R. S., O'Reilly, M. S., Folkman, J., Dvorak, H. F., Brown, L. F., & Berse, B. (1994). Vascular endothelial growth factor/vascular permeability factor is temporally and spatially correlated with ocular angiogenesis in a primate model. *The American Journal of Pathology*, *145*, 574–584.

Nakamura, R., Sene, A., Santeford, A., Gdoura, A., Kubota, S., Zapata, N., & Apte, R. S. (2015). IL10-driven STAT3 signalling in senescent macrophages promotes pathological eye angiogenesis. *Nature Communications*, *6*, 7847. https://doi.org/10.1038/ncomms8847

Nia, H. T., Munn, L. L., & Jain, R. K. (2019). Mapping physical tumor microenvironment and drug delivery. *Clinical Cancer Research*, *25*, 2024–2026. https://doi.org/10.1158/1078-0432.CCR-18-3724

Nishijima, K., Ng, Y. S., Zhong, L., Bradley, J., Schubert, W., Jo, N., Akita, J., Samuelsson, S. J., Robinson, G. S., Adamis, A. P., & Shima, D. T. (2007). Vascular endothelial growth factor-A is a survival factor for retinal neurons and a critical neuroprotectant during the adaptive response to ischemic injury. *The American Journal of Pathology*, *171*, 53–67. https://doi.org/10.2353/ajpath.2007.061237

Novartis. (2015). Clinical trial results: A multicenter, randomized, sham-control, proof-of-concept study of intravitreal LFG316 in patients with geographic atrophy associated with age-related macular degeneration.

Nozaki, M., Raisler, B. J., Sakurai, E., Sarma, J. V., Barnum, S. R., Lambris, J. D., Chen, Y., Zhang, K., Ambati, B. K., Baffi, J. Z., & Ambati, J. (2006). Drusen complement components C3a and C5a promote choroidal neovascularization. *Proceedings of the National Academy of Sciences of the United States of America*, *103*, 2328–2333. https://doi.org/10.1073/pnas.0408835103

Nussenblatt, R. B., Byrnes, G., Sen, H. N., Yeh, S., Faia, L., Meyerle, C., Wroblewski, K., Li, Z., Liu, B., Chew, E., Sherry, P. R., Friedman, P., Gill, F., & Ferris, F. (2010). A randomized pilot study of systemic immunosuppression in the treatment of age-related macular degeneration with choroidal neovascularization. *Retina*, *30*, 1579–1587. https://doi.org/10.1097/IAE.0b013e3181e7978e

PanOptica I. (2019). PanOptica anti-VEGF eye drop shows promise in treatment of neovascular (wet) AMD.

Perez, V. L., & Caspi, R. R. (2015). Immune mechanisms in inflammatory and degenerative eye disease. *Trends in Immunology*, *36*, 354–363. https://doi.org/10.1016/j.it.2015.04.003

Pescina, S., Ostacolo, C., Gomez-Monterrey, I. M., Sala, M., Bertamino, A., Sonvico, F., Padula, C., Santi, P., Bianchera, A., & Nicoli, S. (2018). Cell penetrating peptides in ocular drug delivery: State of the art. *Journal of Controlled Release*, *284*, 84–102. https://doi.org/10.1016/j.jconrel.2018.06.023

Poor, S., Adams, C. M., Ferriere, M., Weichselberger, A., Grosskreutz, C., & Weissgerber, G. (2018). Topical VEGF receptor inhibitor, LHA510, did not demonstrate efficacy in a proof-of-concept study in patients with neovascular age-related macular degeneration (nv AMD). *Investigative Ophthalmology & Visual Science*, *59*, 2394–2394.

Rakoczy, E. P., Lai, C. M., Magno, A. L., Wikstrom, M. E., French, M. A., Pierce, C. M., Schwartz, S. D., Blumenkranz, M. S., Chalberg, T. W., Degli-Esposti, M. A., & Constable, I. J. (2015). Gene therapy with recombinant adeno-associated vectors for neovascular age-related macular degeneration: 1 year follow-up of a Phase 1 randomised clinical trial. *Lancet*, *386*, 2395–2403. https://doi.org/10.1016/S0140-6736(15)00345-1

Ramo, K., Cashman, S. M., & Kumar-Singh, R. (2008). Evaluation of adenovirus-delivered human CD59 as a potential therapy for AMD in a model of human membrane attack complex formation on murine RPE. *Investigative Ophthalmology & Visual Science*, *49*, 4126–4136. https://doi.org/10.1167/iovs.08-2025

Regeneron. (2017). Regeneron provides update on EYLEA® (aflibercept) injection and Nesvacumab (Ang2 antibody) combination program. Regeneron.

Ren, X., Li, J., Xu, X., Wang, C., & Cheng, Y. (2016). IBI302, a promising candidate for AMD treatment, targeting both the VEGF and complement system with high binding affinity in vitro and effective targeting of the ocular tissue in healthy rhesus monkeys. *Experimental Eye Research*, *145*, 352–358.

Robertson, M. J., Kirkwood, J. M., Logan, T. F., Koch, K. M., Kathman, S., Kirby, L. C., Bell, W. N., Thurmond, L. M., Weisenbach, J., & Dar, M. M. (2008). A dose-escalation study of recombinant human interleukin-18 using two different schedules of administration in patients with cancer. *Clinical Cancer Research*, *14*, 3462–3469. https://doi.org/10.1158/1078-0432.CCR-07-4740

Rofagha, S., Bhisitkul, R. B., Boyer, D. S., Sadda, S. R., Zhang, K., & Group S-US. (2013). Seven-year outcomes in ranibizumab-treated patients in ANCHOR, MARINA, and HORIZON: A multicenter cohort study (SEVEN-UP). *Ophthalmology*, *120*, 2292–2299.

Rosenfeld, P. J., Berger, B., Reichel, E., Danis, R. P., Gress, A., Ye, L., Magee, M., Parham, L. R., & McLaughlin, M. M. (2018). A randomized Phase 2 study of an anti-amyloid beta monoclonal antibody in geographic atrophy secondary to age-related macular degeneration. *Ophthalmology Retina*, *2*, 1028–1040. https://doi.org/10.1016/j.oret.2018.03.001

Rosenfeld, P. J., Brown, D. M., Heier, J. S., Boyer, D. S., Kaiser, P. K., Chung, C. Y., & Kim, R. Y. (2006). Ranibizumab for neovascular age-related macular degeneration. *The New England Journal of Medicine*, *355*, 1419–1431. https://doi.org/10.1056/NEJMoa054481

Rosenfeld, P. J., Dugel, P. U., Holz, F. G., Heier, J. S., Pearlman, J. A., Novack, R. L., Csaky, K. G., Koester, J. M., Gregory, J. K., & Kubota, R. (2018). Emixustat hydrochloride for geographic atrophy secondary to age-related macular degeneration: A randomized clinical trial. *Ophthalmology*, *125*, 1556–1567. https://doi.org/10.1016/j.ophtha.2018.03.059

Rosenfeld, P. J., & Feuer, W. J. (2018). Lessons from recent phase III trial failures: Don't design phase III trials based on retrospective subgroup analyses from phase II trials. *Ophthalmology*, *125*, 1488–1491.

Rosenfeld, P. J., Moshfeghi, A. A., & Puliafito, C. A. (2005). Optical coherence tomography findings after an intravitreal injection of bevacizumab (avastin) for neovascular age-related macular degeneration. *Ophthalmic Surgery, Lasers & Imaging*, *36*, 331–335. https://doi.org/10.3928/1542-8877-20050701-14

Ross, C., Engler, C. B., Sander, B., & Bendtzen, K. (2002). IFN-alpha antibodies in patients with age-related macular degeneration treated with recombinant human IFN-alpha2a. *Journal of Interferon & Cytokine Research*, *22*, 421–426. https://doi.org/10.1089/10799900252952208

Sandhu, H. S., Lambert, J., Xu, Y., & Kaplan, H. J. (2018). Systemic immunosuppression and risk of age-related macular degeneration. *PLoS One*, *13*, e0203492.

Scholz, R., Caramoy, A., Bhuckory, M. B., Rashid, K., Chen, M., Xu, H., Grimm, C., & Langmann, T. (2015). Targeting translocator protein (18kDa) (TSPO) dampens pro-inflammatory microglia reactivity in the retina and protects from degeneration. *Journal of Neuroinflammation*, *12*, 201. https://doi.org/10.1186/s12974-015-0422-5

Sharma, R., Khristov, V., Rising, A., Jha, B. S., Dejene, R., Hotaling, N., Li, Y., Stoddard, J., Stankewicz, C., Wan, Q., Zhang, C., Campos, M. M., Miyagishima, K. J., McGaughey, D., Villasmil, R., Mattapallil, M., Stanzel, B., Qian, H., Wong, W., … Bharti, K. (2019). Clinical-grade stem cell-derived retinal pigment epithelium patch rescues retinal degeneration in rodents and pigs. *Science Translational Medicine*, *11*, eaat5580.

Shaw, L. T., Mackin, A., Shah, R., Jain, S., Jain, P., Nayak, R., & Hariprasad, S. M. (2020). Risuteganib-a novel integrin inhibitor for the treatment of non-exudative (dry) age-related macular degeneration and diabetic macular edema. *Expert Opinion on Investigational Drugs*, *29*, 547–554.

Shen, J., Choy, D. F., Yoshida, T., Iwase, T., Hafiz, G., Xie, B., Hackett, S. F., Arron, J. R., & Campochiaro, P. A. (2014). Interleukin-18 has anti-permeablity and antiangiogenic activities in the eye: Reciprocal suppression with VEGF. *Journal of Cellular Physiology*, *229*, 974–983.

Souied, E. H., Devin, F., Mauget-Faysse, M., Kolář, P., Wolf-Schnurrbusch, U., Framme, C., Gaucher, D., Querques, G., Stumpp, M. T., Wolf, S., & MP0112 Study Group. (2014). Treatment of exudative age-related macular degeneration with a designed ankyrin repeat protein that binds vascular endothelial growth factor: A phase I/II study. *American Journal of Ophthalmology*, *158*, 724–732.e722

Takahashi, K., Saishin, Y., Saishin, Y., King, A. G., Levin, R., & Campochiaro, P. A. (2009). Suppression and regression of choroidal neovascularization by the multitargeted kinase inhibitor pazopanib. *Archives of Ophthalmology*, *127*, 494–499. https://doi.org/10.1001/archophthalmol.2009.27

Theodoropoulou, S., Copland, D. A., Liu, J., Wu, J., Gardner, P. J., Ozaki, E., Doyle, S. L., Campbell, M., & Dick, A. D. (2017). Interleukin-33 regulates tissue remodelling and inhibits angiogenesis in the eye. *The Journal of Pathology*, *241*, 45–56. https://doi.org/10.1002/path.4816

Therapeutics LC. (2020). Lineage cell therapeutics presents new OpRegen® data for dry AMD with GA at 2020 American Academy of Ophthalmology Annual Meeting.

Tsujinaka, H., Fu, J., Shen, J., Yu, Y., Hafiz, Z., Kays, J., McKenzie, D., Cardona, D., Culp, D., Peterson, W., Gilger, B. C., Crean, C. S., Zhang, J. Z., Kanan, Y., Yu, W., Cleland, J. L., Yang, M., Hanes, J., & Campochiaro, P. A. (2020). Sustained treatment of retinal vascular diseases with self-aggregating sunitinib microparticles. *Nature Communications*, *11*, 694. https://doi.org/10.1038/s41467-020-14340-x

Unity Biotechnology I. UNITY biotechnology announces completion of UBX1967 license and advance into IND-enabling studies for age-related diseases of the eye. https://ir.unitybiotechnology.com/news-releases/news-release-details/unity-biotechnology-announces-completion-ubx1967-license-and; 03-01-2019.

von der Emde, L., Pfau, M., Dysli, C., Thiele, S., Möller, P. T., Lindner, M., Schmid, M., Fleckenstein, M., Holz, F. G., & Schmitz-Valckenberg, S. (2019). Artificial intelligence for morphology-based function prediction in neovascular age-related macular degeneration. *Scientific Reports*, *9*, 11132. https://doi.org/10.1038/s41598-019-47565-y

Willcox, M. D., Morris, C. A., Thakur, A., Sack, R. A., Wickson, J., & Boey, W. (1997). Complement and complement regulatory proteins in human tears. *Investigative Ophthalmology & Visual Science*, *38*, 1–8.

Wolf, A., Herb, M., Schramm, M., & Langmann, T. (2020). The TSPO-NOX1 axis controls phagocyte-triggered pathological angiogenesis in the eye. *Nature Communications*, *11*, 2709. https://doi.org/10.1038/s41467-020-16400-8

Wong, W. L., Su, X., Li, X., Cheung, C. M. G., Klein, R., Cheng, C. Y., & Wong, T. Y. (2014). Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: A systematic review and meta-analysis. *The Lancet Global Health*, *2*, e106–e116. https://doi.org/10.1016/S2214-109X(13)70145-1

Wu, J., & Sun, X. (2019). Complement system and age-related macular degeneration: Drugs and challenges. *Drug Design, Development and Therapy*, *13*, 2413–2425. https://doi.org/10.2147/DDDT.S206355

Xi, H., Katschke, K. J. Jr., Li, Y., Truong, T., Lee, W. P., Diehl, L., Rangell, L., Tao, J., Arceo, R., Eastham-Anderson, J., Hackney, J. A., Iglesias, A., Cote-Sierra, J., Elstrott, J., Weimer, R. M., & van Lookeren Campagne, M. (2016). IL-33 amplifies an innate immune response in the degenerating retina. *The Journal of Experimental Medicine*, *213*, 189–207. https://doi.org/10.1084/jem.20150894

Xu, L., Mrejen, S., Jung, J. J., Gallego-Pinazo, R., Thompson, D., Marsiglia, M., & Freund, K. B. (2015). Geographic atrophy in patients receiving anti-vascular endothelial growth factor for neovascular age-related macular degeneration. *Retina*, *35*, 176–186. https://doi.org/10.1097/IAE.0000000000000374

Yafai, Y., Yang, X. M., Niemeyer, M., Nishiwaki, A., Lange, J., Wiedemann, P., King, A. G., Yasukawa, T., & Eichler, W. (2011). Anti-angiogenic effects of the receptor tyrosine kinase inhibitor, pazopanib, on choroidal neovascularization in rats. *European Journal of Pharmacology*, *666*, 12–18. https://doi.org/10.1016/j.ejphar.2011.05.016

Yaspan, B. L., Williams, D. F., Holz, F. G., Regillo, C. D., Li, Z., Dressen, A., van Lookeren Campagne, M., le, K. N., Graham, R. R., Beres, T., Bhangale, T. R., Honigberg, L. A., Smith, A., Henry, E. C., Ho, C., Strauss, E. C., & for the MAHALO Study Investigators. (2017). Targeting factor D of the alternative complement pathway reduces geographic atrophy progression secondary to age-related macular degeneration. *Science Translational Medicine*, *9*(395), eaaf1443. https://doi.org/10.1126/scitranslmed.aaf1443

Yates, J. R., Sepp, T., Matharu, B. K., Khan, J. C., Thurlby, D. A., Shahid, H., Clayton, D. G., Hayward, C., Morgan, J., Wright, A. F., Armbrecht, A. M., Dhillon, B., Deary, I. J., Redmond, E., Bird, A. C., Moore, A. T., & Genetic Factors in AMD Study Group. (2007). Complement C3 variant and the risk of age-related macular degeneration. *The New England Journal of Medicine*, *357*, 553–561.

Yehoshua, Z., de Amorim Garcia Filho, C. A., Nunes, R. P., Gregori, G., Penha, F. M., Moshfeghi, A. A., Zhang, K., Sadda, S., Feuer, W., & Rosenfeld, P. J. (2014). Systemic complement inhibition with eculizumab for geographic atrophy in age-related macular degeneration: The COMPLETE study. *Ophthalmology*, *121*, 693–701. https://doi.org/10.1016/j.ophtha.2013.09.044

Yim, J., Chopra, R., Spitz, T., Winkens, J., Obika, A., Kelly, C., Askham, H., Lukic, M., Huemer, J., Fasler, K., Moraes, G., Meyer, C., Wilson, M., Dixon, J., Hughes, C., Rees, G., Khaw, P. T., Karthikesalingam, A., King, D., … de Fauw, J. (2020). Predicting conversion to wet age-related macular degeneration using deep learning. *Nature Medicine*, *26*, 892–899. https://doi.org/10.1038/s41591-020-0867-7

Ying, M. P. W., Yu, Y., Kays, J., Cardona, D., Culp, D., Gilger, B., & Cleland, J. (2016). GB-102 for wet AMD: A novel injectable formulation that safely delivers active levels of sunitinib to the retina and

RPE/choroid for over four months. *Investigative Ophthalmology & Visual Science*, 57, 5037.

Yoshida, T., Ohno-Matsui, K., Ichinose, S., Sato, T., Iwata, N., Saido, T. C., Hisatomi, T., Mochizuki, M., & Morita, I. (2005). The potential role of amyloid beta in the pathogenesis of age-related macular degeneration. *The Journal of Clinical Investigation*, 115, 2793–2800. https://doi.org/10.1172/JCI24635