Progress in Retinal and Eye Research 99 (2024) 101243

Contents lists available at ScienceDirect

Progress in Retinal and Eye Research

journal homepage: www.elsevier.com/locate/preteyeres

Investing in vision: Innovation in retinal therapeutics and the influence on venture capital investment

Dmitrij Hristodorov [a,1,*], Tim Lohoff [a,1], Nanna Luneborg [b], Geert-Jan Mulder [b], Simon J. Clark [c,d,e]

[a] Forbion, Munich, Germany
[b] Forbion, Naarden, the Netherlands
[c] Institute for Ophthalmic Research, Department for Ophthalmology, University Medical Center, Eberhard Karls University of Tübingen, Tübingen, Germany
[d] University Eye Clinic, University Hospital Tübingen, Tübingen, Germany
[e] Lydia Becker Institute of Immunology and Inflammation, Faculty of Biology, Medicine, and Health, University of Manchester, Manchester, UK

A B S T R A C T

Since the groundbreaking approval of the first anti-VEGF therapy in 2004, the retinal therapeutics field has undergone a remarkable transformation, witnessing a surge in novel, disease-modifying therapeutics for a broad spectrum of retinal diseases, extending beyond exudative VEGF-driven conditions. The surge in scientific advancement and the pressing, unmet, medical need have captured the attention of venture capital investors, who have collectively invested close to $10 billion in research and development of new retinal therapeutics between 2004 and 2023. Notably, the field of exudative diseases has gradually shifted away from trying to outcompete anti-VEGF therapeutics towards lowering the overall treatment burden by reducing injection frequency. Simultaneously, a new era has emerged in the non-exudative field, targeting prevalent conditions like dry AMD and rare indications such as Retinitis pigmentosa. This has led to promising drug candidates in development, culminating in the landmark approval of Luxturna for a rare form of Retinitis pigmentosa. The validation of new mechanisms, such as the complement pathway in dry AMD has paved the way for the approvals of Syvovre (Apellis) and Izervay (Iveric/Astellas), marking the first two therapies for this condition. In this comprehensive review, we share our view on the cumulative lessons from the past two decades in developing retinal therapeutics, covering both positive achievements and challenges. We also contextualize the investments, strategic partnering deals, and acquisitions of biotech companies, pharmaceutical companies venture capital investors in retinal therapeutics, respectively. Finally, we provide an outlook and potentially a forward-looking roadmap on novel retinal therapeutics, highlighting the emergence of potential new intervention strategies, such as cell-based therapies, gene editing, and combination therapies. We conclude that upcoming developments have the potential to further stimulate venture capital investments, which ultimately could facilitate the development and delivery of new therapies to patients in need.

1. Innovation in retinal drug development started with anti-VEGF

The development of anti-vascular endothelial growth factor (anti-VEGF) drugs has revolutionized the treatment of various retinal conditions, where excessive blood vessel growth and vessel leakage are major contributors to disease pathogenesis. The therapeutic implications of anti-angiogenesis were first recognized in the field of oncology in the 1970s (Sherwood et al., 1971; Gimbrone et al., 1972). However, it was not until the FDA approval of the anti-VEGF aptamer Pegatanib (Macugen) in 2004 that anti-VEGF agents made their way into ophthalmic clinical practice, which was a paradigm shift in the treatment of retinal disease. Subsequently, bevacizumab (Avastin) and ranibizumab (Lucentis), both originally investigated for the treatment of cancer, also showed impressive benefits in ophthalmic applications (Krzystolik et al., 2002). In 2005, Philip Rosenfeld et al. used bevacizumab in patients with wet age-related macular degeneration (AMD) and reported positive outcomes, which contributed to the broader recognition of its efficacy (Rosenfeld et al., 2005). Over the years, the use of anti-VEGF agents has expanded, leading to the investigation of these drugs in the context of various retinal diseases, including AMD, diabetic macular edema (DME), retinal vein occlusion (RVO), proliferative diabetic retinopathy (PDR), retinopathy of prematurity (ROP), polypoidal choroidal vasculopathy (PCV), and choroidal neovascularization (CNV) (Cornel et al., 2015; Kim and D'Amore, 2012; Ng et al., 2006) (Fig. 1).

* Corresponding author.
E-mail address: dmitrij.hristodorov@forbion.com (D. Hristodorov).
[1] Equally contributed to the manuscript.

https://doi.org/10.1016/j.preteyeres.2024.101243
Received 31 October 2023; Received in revised form 6 January 2024; Accepted 8 January 2024
Available online 12 January 2024

Abbreviations

A2E	Bis-retinoid N-retinyl-N-retinylidene ethanolamine
AAV	Adeno-associated virus
Ab	Antibody
ABCA4	ATP-binding cassette transporter 4
AMD	Age-related macular degeneration
Ang2	Angiopoietin 2
ASO(s)	Anti-sense oligonucleotide(s)
BCVA	Best corrected visual acuity
BrM	Bruch's membrane
C3	Complement component 3
C5	Complement component 5
CFH	Gene encoding Complement Factor H
CFI	Gene encoding Complement Factor I
CNV	Choroidal neovascularization
CRISPR	Clustered regulatory interspaced short palindromic repeats
DME	Diabetic macular edema
DR	Diabetic retinopathy
ECM	Extracellular matrix
FDA	Food and Drug Administration
FH	Complement Factor H
FHL-1	Factor H-like protein 1
FHR	Factor H-related protein
FI	Complement Factor I
GA	Geographic atrophy
HD	High-dose
IRD	Inherited retinal degeneration
IVT	Intravitreal
kb	kilobases
LCA	Leber congenital amaurosis
LNP(s)	Lipid nanoparticle(s)
MAC	Membrane attack complex
OCT	Optical coherence tomography
PCV	Polypoidal choroidal vasculopathy
PDGF	Platelet derived growth factor
PDR	Proliferative Diabetic Retinopathy
ROP	Retinopathy of prematurity
RP	Retinitis pigmentosa
RPE	Retinal pigment epithelium
RVO	Retinal vein occlusion
STGD	Stargardt disease
VC	Venture Capital
VEGF	Vascular endothelial growth factor

1.1. Macugen, Avastin, and the search for next-generation intravitreal anti-VEGF drugs

The field of ophthalmology could celebrate the first significant successes in bringing therapeutic treatment options to patients with retinal degenerative diseases with the approval of Macugen in 2004. Although this product never became a commercial success, the introduction of the class of anti-VEGF drugs for treating vascular retinal diseases led to substantial benefits for patients, significant financial rewards for the pharma industry, and spurred new investment and development efforts by venture capital (VC) and biotech companies. Also in 2004, another ant-VEGF drug, the humanized anti-VEGF monoclonal antibody Avastin (Bevacizumab), became FDA approved for the treatment of previously untreated metastatic colorectal cancer after successfully slowing the growth of solid tumors (Presta et al., 1997). Indeed, Avastin remains today one of the most widely used cancer therapeutics for multiple indications (Garcia et al., 2020). Avastin has been used off-label for several years to treat CNV associated with wet AMD following Phil Rosenfeld's pioneering work in ocular diseases around 2005. However, this use is not without controversy as the makers of Avastin (Genentech/Roche) also made Lucentis (ranibizumab), another anti-VEGF treatment that is FDA approved for use in AMD, since 2006. The controversy lies in the cost of administration between the two drugs, where Avastin costs ~$50 per injection (when splitting cancer treating doses into smaller doses for ocular treatments) as opposed to the ~$2000 per injection of Lucentis (Raftery et al., 2007): there are no signs that Genentech/Roche intends to present Avastin to the FDA for approval in AMD any time soon which has raised a discussion around the economic disparity in eye health (Moreno and Kim, 2016). In the meantime, Outlook Therapeutics is trying to secure approval for a fully ophthalmic formulation of bevacizumab (the active pharmaceutical ingredient behind Avastin) (Outlook Therapeutics, 2023). A recently published nice review describes the history around the use of anti-VEGF drugs in cancer, and off-label in ophthalmology (Cao et al., 2023). Nevertheless, since 2006, Lucentis dominated the CNV field for more than a decade. These successful products triggered competition for improved VEGF-targeted therapies, such as aflibercept (Eylea), which led to a license and collaboration agreement between the originator of aflibercept, Regeneron, and the new kid on the block in the ocular business, Bayer Pharma, in 2006. Although this positive drive for innovation and collaboration stuttered in the global financial crisis in 2008, along with all other therapeutic areas beyond ophthalmology, by 2012, financial markets started to recover, public offerings became possible again, and Regeneron and Bayer achieved another big milestone in the short history of drug development in retinal disease, by receiving Food and Drug Administration (FDA) and European Medicines Agency approval for Eylea with an improved treatment posology compared to the established standard-of-care Lucentis. In two Phase 3 clinical studies (VIEW 1,

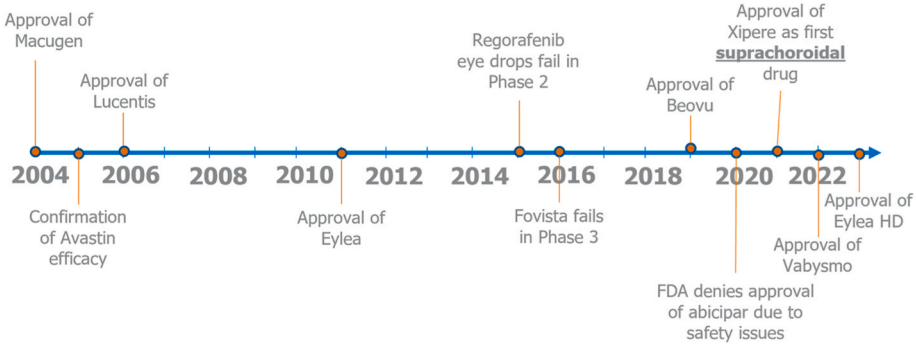


Fig. 1. A brief history of key milestones of anti-VEGF drugs. Illustration of key milestones, positive and negative, on the way to several approved drugs for exudative retinal diseases from 2004 until today.

NCT00509795 and VIEW 2, NCT00637377), Eylea showed similar efficacy at less frequent intravitreal (IVT) dosing (Q8W) compared to Lucentis (Q4W) (Heier et al., 2012). With the approval of a second anti-VEGF agent in wet AMD, at least three general approaches in research and development entered the competition: (1) product candidates aiming to beat anti-VEGF drugs in efficacy, and (2) product candidates that could reduce the treatment burden of frequent intraocular injections; and (3) addressing anti-VEGF suboptimal/non-responders.

1.2. Next-generation targeted therapies

To produce a superior drug to the clinically used anti-VEGF drugs, researchers have explored two strategies: (1) targeting an orthogonal pathway to VEGF-mediated inflammation and vascular leakage, and/or (2) a combination of one of the anti-VEGF drugs with a new orthogonal mechanism. The goal was either to show superior vision gains and/or drying of the retina, mainly in anti-VEGF treatment naïve patients, or address suboptimal-/non-responders to anti-VEGF, which is not a well-defined patient population. While several approaches were able to show differentiation and superiority in preclinical models (mainly laser-induced CNV models), ultimately none could beat existing anti-VEGF drugs in larger clinical trials. In 2009, Novartis' affiliate company Alcon, acquired a single-chain fragment variable (scFv) antibody (Ab) fragment-based asset, brolicizumab, for an upfront consideration of $150 million, and a further $439 million in milestones, from the Swiss biotech ESBATech. Brolicizumabis yet another anti-VEGF targeted therapy, which due to its protein format (scFv, 26 kDa) is smaller in size than e.g. Lucentis which is a Fab fragment (48 kDa), or Eylea which is an Fc-fusion trap protein (115 kDa). Brolicizumab had demonstrated promising clinical results of increased drying of the retina and potentially longer durability, allowing less frequent administration, in Phase 3 studies (KITE, NCT03481660 and KINGFISHER, NCT03917472), and which achieved FDA approval in 2019 as Beovu. One of the hypotheses as to why Beovu could be superior while still being an anti-VEGF was based on its increased solubility and its smaller size which could potentially result in higher penetration of retinal tissues in patients – a hypothesis that cannot be proven in vivo in humans (Nguyen et al., 2020; Martin et al., 2012). However, safety concerns around intraocular inflammation (Baumal et al., 2020; Haug et al., 2020) led to a disappointing commercial outcome for Beovu, and Novartis reported a modest ~$200 million in sales revenue in 2022 (Fig. 4B). Beovu stands as an example for drugs that made it far in the value chain of drug development and yet could not become a commercial success for the Pharma companies. With increasing segmentation of the retinal therapeutics market, especially for drugs addressing diseases such as wet AMD and DME, the bar for efficacy rises together with the bar for safety. Successful drugs like Lucentis and Eylea have created a high standard for safety and neither patients nor physicians nor regulatory can and will accept anything inferior. Increased cases of intra-ocular inflammation are high on the list for scrutiny and can decide the fate of a drug in the end. From an VC investment and Pharma acquisition perspective though it is difficult to predict the ultimate safety of such drugs due to the overall low even rates which often cannot be reliably assessed in Phase 2 studies (Knickelbein et al., 2016; Schmidt-Ott et al., 2023). At the same time, programs & biotech companies with Phase 2 data are typically high on the list of acquisition candidates.

The second strategy to beat anti-VEGF has also been ultimately disappointing, with multiple failures and few companies still in the race. A high-profile example of this was Ophthotech's anti-platelet derived growth factor (PDGF) aptamer, pegpleranib (Fovista) (Carroll, 2014). In 2012, Ophthotech published data from a Ph2b study in 449 patients, demonstrating superior vision gain in combination with Lucentis, compared to Lucentis alone. This led to a licensing deal between Ophthotech and Novartis for ex-US rights in 2014 ($200 million upfront, up to $1 billion in milestones, ex-US rights only) to develop a combination therapy of Lucentis and Fovista. With the goal of superior efficacy in mind, an increased injection burden was deemed acceptable, as the two drugs had to be administered in two separate injections 30 min apart. Despite a sound biological rationale and Phase 2 b data in hands, improved efficacy could not be demonstrated in two subsequent Phase 3 studies (OPH1002 and OPH1003, NCT01944839 and NCT01940900 respectively), which together included more than 1200 patients. This was also the end of Ophthotech, which went through a strategic re-set and restarted as Iveric in 2019. The sizeable deal between Novartis and Ophthotech pre-Phase 3 data could have been fuelled by competitive pressure generated by Regeneron. Regeneron was developing its own anti-VEGF/PDGF combo drug composed of aflibercept and rinucumab which, however, similar to Fovista, did not show a benefit in a Phase 2 study in wet AMD in 2016 (Regeneron, 2016). Both deals Alcon/ESBATech (Beovu) and Ophthotech/Novartis (Fovista) are part of the top 10 deals (based on total deal value and upfront payment) in retinal business in the past two decades (Table 1), but ultimately did not lead to success.

The Australian company Opthea is also pursuing a combination approach to improve on the treatment benefit from anti-VEGF alone, with the initial goal of addressing anti-VEGF suboptimal/non-responders, by adding a second injection with a biological trap molecule (similar to Eylea in format) that targets VEGF-C and -D, instead of VEGF-A as it is the case for Lucentis, Eylea, and Avastin. In fact, anti-VEGF suboptimal/non-responders constitute a large proportion of all wet AMD and DME patients. Depending on the exact definition of a non-responder and the profile of the patient, non-response numbers can be found in the range of ~30% for DME and up to ~67% in wet AMD (Martin et al., 2012; JA et al., 2015; Romero-Aroca et al., 2016). In 2022, Opthea entered into a strategic financing agreement with Launch Therapeutics, a development company formed and managed by the private equity firm Carlyle and its life science franchise, Abingworth, to fund pivotal studies in wet AMD (ShORe, NCT04757610 and COAST, NCT04757636). Results from these trials are expected in 2023/24.

In parallel to these attempts to enhance the treatment benefit of current anti-VEGF drugs, pharma, and biotech started to explore more convenient therapy, as frequent intraocular injections present a significant treatment burden. Real-world evidence for anti-VEGF agents in clinical practice, outside the controlled setting of a clinical trial, has shown that the majority of patients are not compliant with the recommended frequency of injections, and are not achieving the same

Table 1
Summary of the 10 largest deals including mergers and acquisitions and licensing transactions of retinal therapeutics companies since 2004.
The table is sorted by total deal value.

Target Company	Acquirer	Key asset/ indication	Year	Upfront	Total Deal Value
Iveric	Astellas	Izervay/dry AMD/ GA	2023	$5.9 billion	$5.9 billion
Spark	Roche	Luxturna/retinitis pigmentosa	2019	$4.8 billion	$4.8 billion
Regenxbio	Abbvie	RGX-314/wet AMD	2021	$370 million	$1.75 billion
Gyroscope	Novartis	GT005/dry MAD/ GA	2021	$800 million	$1.5 billion
Ophthotech	Novartis	Fovista/wet AMD	2014	$200 million	$1.03 billion
Nightstar	Biogen	NSR-REP1/ choroideremia	2019	$877 million	$877 million
ESBATech	Alcon	Brolicizumab/wet AMD	2009	$150 million	$439 million
Vedere Bio I	Novartis	Optogenetic platform/IRDs	2020	$150 million	$430 million
Ocata	Astellas	RPE cells/Stargardt & dry AMD/GA	2015	$379 million	$379 million
Spark	Novartis	Luxturna/retinitis pigmentosa	2018	$105 million	$170 million

magnitude of treatment benefit as shown in Phase 3 studies (Chong, 2015).

Two recent approvals mark incremental success in more durable anti-VEGF-driven treatment, with reduced treatment burden, Vabysmo and Eylea High-Dose (HD).

Vabysmo: Despite the failure of Bayer and Regeneron, through their renewed $50 million upfront R&D pact signed in 2016, to demonstrate in Phase 2 that combining Eylea with an investigational anti-Angiopoietin 2 (Ang2) Ab can improve outcomes, a bi-specific Ab targeting the same two targets (VEGF-A and Ang2) called Vabysmo (faricimab) had been developed by Roche. Vabysmo was recently approved based on multiple Phase 3 studies (TENAYA and LUCERNE, NCT03823287 and NCT03823300 respectively) showing increased durability as compared to Eylea. Vabysmo could achieve that 72–79% and 45–52% of patients could be extended to Q12W and Q16W dosing intervals, respectively.

Eylea-HD: In addition to blocking Ang2 in concert with VEGF, one further hypothesis why for example Beovu and Vabysmo have shown slightly better durability, is the lower molecular weight of the molecule, allowing increased molarity of the drug in one dose. Following this principle, Regeneron & Bayer generated a high-dose formulation of Eylea and only recently received FDA approval for wet AMD, DME, and DR, demonstrating similar durability as their rivals from Switzerland. This approval was based on two pivotal studies (PHOTON and PULSAR, NCT04429503 and NCT04423718, respectively) which showed that 79–91% and 77–89% of patients could be extended to Q12W and Q16W dosing intervals, respectively. This result, also considering the more stringent trial design for Eylea-HD vs Vabysmo's Phase 3 studies in terms of when patients were randomized, can be seen as a clear win for Regeneron & Bayer. In 2023, Regeneron & Bayer provided an update on two-year results from both PUSLAR and PHOTON trials for Eylea-HD, demonstrating that 43–47% of patients met extension criteria for 20 or more weeks of durability and 27–28% for 24-week intervals (Regeneron, 2023a; Regeneron, 2023b).

2. Alternative delivery strategies – intravitreal remains king

The quest for more convenient treatments has led to assessments of multiple different approaches, such as eye drops, IVT non-biodegradable/refillable or biodegradable slow-release implants, and oral small molecules (Rafael et al., 2023). Numerous clinical studies have been conducted with various (re)-formulations of small molecule drugs designed for topical administration. The results are sobering: none of the eye drop-delivered treatments came close to the efficacy level of IVT-administered anti-VEGF drugs (Csaky et al., 2015; Joussen et al., 2019). Frustratingly, it is also difficult to learn from these failures, given that one cannot easily sample tissue in ocular trials to gain information on drug pharmacokinetics and pharmacological target engagement. Multiple programs, such as PAN-90806 from PanOptica (PanOptica), Regorafenib from Bayer Pharma (Joussen et al., 2019), and more recently EXN-407 from Exonate (partnered with J&J) never progressed to registrational studies (Ellis, 2023). Oral drugs as a class still hold promise as a non-invasive, early intervention option to treat retinal diseases. Several first-mover approaches have faced challenges in clinical development, often accompanied by complicated clinical trial designs and commercial positioning, such as maintenance therapy after initial loading doses of IVT anti-VEGF injections. Companies such as Tyrogenex (Cohen et al., 2021; Alkahest), and others have either terminated studies at various stages of development due to underwhelming results or have simply not reported any significant progress for many years. Nevertheless, there is still hope for companies like KalVista and Ocuphire, the latter preparing an oral Ref1 inhibitor called APX-3330 for the treatment of DR (Ocuphire Pharma, 2023).

An alternative approach to reduce the treatment burden was IVT implants. A prominent example of a non-biodegradable & refillable implant is Susvimo from Roche/Genentech. Roche/Genentech initially acquired the refillable port delivery system for sustained delivery of ranibizumab from ForSight Vision4 in 2017 for an undisclosed amount (ForSight VISION4 Inc., 2017). The anticipated durability profile was a refill every six months which at that time would have exceeded the durability of any other anti-VEGF agent. Following positive outcomes from the Phase 2 LADDER study (NCT02510794 (Khanani et al., 2021);) and the Phase 3 Archway study (NCT03677934; (Holekamp et al., 2022), Susvimo was approved by the FDA in 2021. Since approval, Susvimo faced strong headwinds as far as its adoption is concerned resulting in sale volumes way below initial expectations (Jonathan Gardner, 2021). The key driver of this outcome is the increased safety risk compared to drugs like Eylea given that Susvimo requires an initial surgery and was associated with various adverse events in the Archway study which can be avoided by using Eylea, for example (Adams, 2022).

The other IVT slow-release concept is to use biologically degradable implants, often based on a lactate-based polymeric formulation (Alshaikh et al., 2022). GrayBug Therapeutics and Ocular Therapeutix were, amongst others, pioneering this approach. While the drug substance did target a plethora of different tyrosine kinase receptors including the validated biological pathway driven by VEGF, using small molecule tyrosine kinase inhibitors, such as sunitinib or axitinib, the key challenge was to tune the implant for a biphasic release profile, allowing an initial fast release of the drug to achieve an induction therapy effect, while simultaneously providing continuous, slow release to achieve durability of at least six months. Unfortunately, it turned out that the physicochemical properties of the implant in human eyes were different than expected, based on *in vitro* or animal models, and treatment resulted in either unexpected safety issues (e.g. movement of implant debris into the anterior chamber), too slow or too fast release of the drug, and ultimately in failure to achieve the envisioned target product profile. Recently, Kodiak Sciences, which employed an Ab conjugate format of an anti-VEGF drug to achieve longer injection intervals in multiple indications including DME and NPDDR, also had to declare defeat and discontinue further development upon disappointing clinical results (Kodiak Sciences, 2023). The company mentioned that increased cataract formation in the treatment group might have created an imbalance between groups and contributed to the inferior best corrected visual acuity (BCVA) outcomes. Interestingly, only a few months later the company announced a reboot of its lead program tarcocimab in moderately-severe NPDR following further analyses from BEACON and GLOW studies and supported by FDA guidance (Kodiak Sciences Inc, 2023).

Despite multiple clinical trials, IVT pharmacokinetics remain poorly understood in ocular drug development. In contrast to the vitreous as the target compartment for drugs, companies like Clearside Biomedical and Oxular have opted for another intraocular cavity and developed delivery and formulation technologies that enable the placement of drugs into the much more contained suprachoroidal space (Wan et al., 2021). Both companies have developed proprietary injection devices that allow them to access this space in a relatively non-invasive fashion, allowing in-office administration. Clearside has advanced this technology into clinical assessments in several indications internally and with partners and has achieved initial approval of a product partnered with Bausch & Lomb. Oxular has developed what the company believes to be a differentiated device design, which enables (1) a truly posterior placement of the drug (closer to the macula, as opposed to a rather anterior placement by Clearside), and (2) higher precision control guided by a light source, potentially resulting in fewer suprachoroidal mis-injections. The clinical safety and efficacy of both technologies will be evaluated soon given that both companies are conducting clinical trials at the time of writing this review.

3. Gene therapy to deliver VEGF-inhibitors

The next chapter in the story of VEGF-modulation to treat retinal disease may be to replace frequent IVT injections with gene therapy. The

concept of gene therapy, or more specifically of gene correction, is better known from inherited genetic diseases where a one-time administration of the new gene is aimed at supplying a functional version of the defective gene. We will discuss this in more detail below in the inherited retinal degeneration section. In the case of VEGF-modulation, though, gene therapy is meant to represent a bio-factory approach whereby a therapeutic molecule (i.e. anti-VEGF antibody/trap) is being constitutively produced in the eye. Clinical-stage examples are Regenxbio and Adverum, both having advanced clinical programs, using an adeno-associated virus (AAV) vector to encode a VEGF-inhibitor and have demonstrated continued expression of the VEGF-inhibitor over multiple years in patients, with the ultimate aim to reduce or eliminate the need for additional injections. Regenxbio is evaluating both subretinal administration and suprachoroidal administration. While the concept of a bio-factory is in fact a very elegant one, it is fair to say that in reality it is way more nuanced as far as efficacy, need for additional intravitreally administered anti-VEGF drugs, and safety (e.g. intra-ocular inflammation, pigmentary changes) are concerned (REGENXBIO, 2021; Avery 2021). These critical clinical observations might stem from the viral vector chosen, from the route of administration in combination with the viral vector chosen, from expression levels of the transgene, etc. In any case, these are important considerations for the commercial success of a drug, as we have seen and learned from intravitreal drugs, such as Beovu, discussed above.

4. Positive outlook for exudative diseases

The last two decades in retinal research for exudative diseases have yielded several important new products that have totally changed the patient journey. Despite multiple setbacks to further improve the established standard of care, there is a rich pipeline of continued innovation to improve treatment options for patients with exudative retinal disease, with multiple investigational drugs leveraging different biological targets, modalities, and administration routes (Fig. 2).

The diverse range of modalities in clinical evaluation spans from classical small molecules and antibodies to anti-sense oligonucleotides (ASOs) and viral gene therapies. This is a testimony to retinal research being at the forefront of innovation in the application of novel technologies. Admittedly, the largest body of experience with retinal therapeutics is with antibody-based drugs and way less with new modalities like ASOs or viral vectors. This carries a still significant risk for drug development and we will likely continue to see a lot of learnings going forward. Assuming continuous ability to raise funding from VC funds and public investors, however, the pipeline depicted in Figs. 2 and 3 could bring a bright future of new clinical and commercial successes for exudative retinal diseases. Should the envisioned drug profiles prove their claims with regard to efficacy and safety, millions of patients could ultimately benefit from better treatment options. Several near-to-mid-term major read-outs and/or regulatory decisions are expected to occur in the coming 4–5 years for wet AMD and DME (Fig. 3).

Finally, the anti-VEGF era in ophthalmology is not only a clinical success in providing optionality to patients and physicians. Depending on the individual situation of the patient, the physician may choose from an extraordinary selection of efficacious anti-VEGF drugs (Fig. 4A). Beyond clinical success and the well-being of patients, anti-VEGF drugs have also delivered attractive returns to Pharma companies commercializing those. Lucentis, Eylea (including Eylea-HD), and Vabysmo are without doubt large blockbuster brands fuelling the revenue books of Roche, Novartis, Regeneron, and Bayer (Fig. 4B). Interestingly, although difficult to calculate accurately, annual sales of Avastin in the US used off-label can be estimated at around $300 million (assuming ~50% patient share, $68 as CMS price, and similar injection frequency as Lucentis).

5. Dry AMD/GA – excitement, resilience, and first successes

The dry form of AMD can be categorized into three severity stages: early, intermediate, and late. The clinical manifestation of the late form is characterized by islands of defined cell death, known as geographic atrophy (GA), that begin around the fovea (in the perifovea belt) and eventually ingress into the fovea itself (Fleckenstein et al., 2018). Once the fovea is affected, patients suffer from severe vision loss ultimately leading to legal blindness. While wet AMD patients have multiple approved anti-VEGF agents as potential treatment options, and the opportunity to switch from one agent to another in case of suboptimal response, physicians until recently had nothing to offer dry AMD/GA patients. Multiple factors have complicated the development of effective therapies in dry AMD/GA: (1) Dry AMD/GA disease etiology is not well understood, although recent advances have highlighted the role of the complement system (as recently reviewed in Armento et al., 2021); (2) dry AMD/GA is a progressive, degenerative disease, meaning that slowing down disease progression can make patients lose sight more slowly, but does not bring back vision already lost. This can be a difficult proposition for expectation management vis-à-vis treatment burden for patients; and (3) the field has suffered from a lot of negative sentiment driven by clinical failures, each of them with their own specific, potential explanations.

5.1. Genetic link between innate immunity and GA

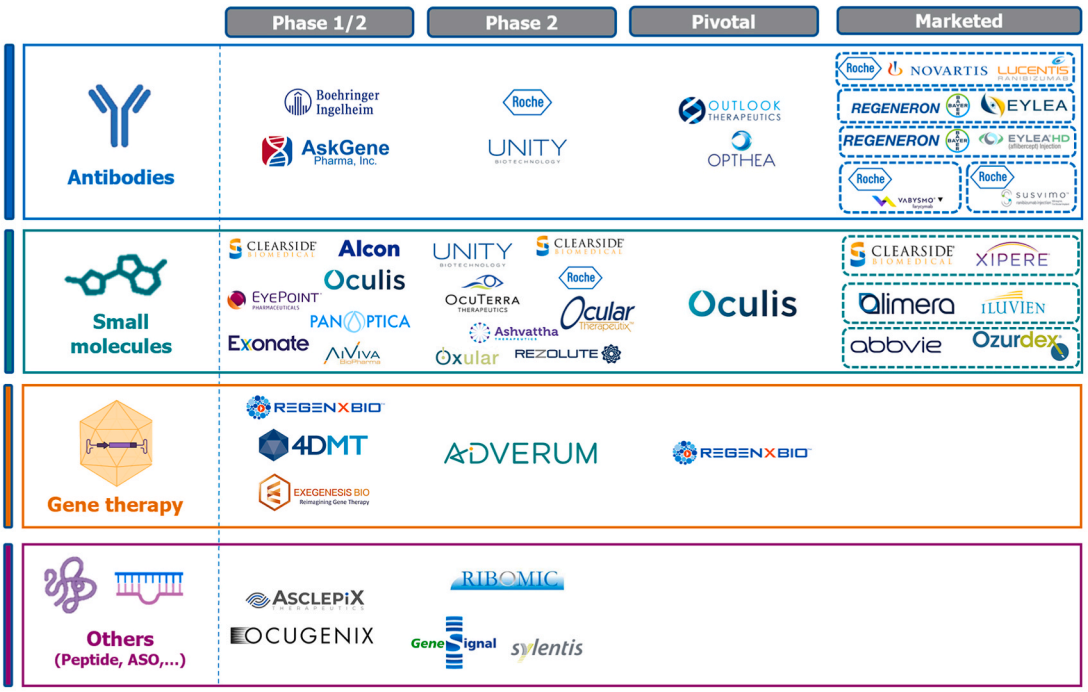
The role of innate immunity in the etiology of AMD was established in 2005 in a series of genetic studies linking variants in the genes of the complement system to increased risk of developing AMD (Haines et al., 2005; Edwards et al., 2005; Klein et al., 2005; Hageman et al., 2005). A particular link was established to a polymorphism in the gene encoding a major regulator of complement activation, complement factor H (CFH). The complement system is a central part of the innate immune system and its intricate protein-protein interaction cascade, its role in health and disease, and how it may be targeted therapeutically, have been described in detail elsewhere (Parente et al., 2017; Rathi et al., 2023; de Jong et al., 2023). The first genetic variant of the CFH gene described was the Y402H polymorphism identified originally in 1988 by a team of researchers in Oxford (Day et al., 1988; Ripoche et al., 1988). At the time it was not known if the Y402H polymorphism had any biochemical consequence at the protein level or any disease association. However, in 2006, one year after the genetic link to AMD, preliminary biochemical studies that showed these genetic variants in CFH altered the ability of the Complement Factor H (FH) protein to recognize and interact with specific sugar molecules, called glycosaminoglycans, on the ECM (Prosser et al., 2007; Clark et al., 2006) including the Bruch's membrane (BrM) in human eyes Clark et al., 2010, 2013). The binding of FH to these sugars is vital for its function as the protector of ECM from aberrant complement overactivation. This finding opened a new area of research into complement activation in the back of the eye in AMD.

Over the subsequent decade of academic and clinical research, our understanding of AMD progression evolved and refined with notable discoveries, including that genetic risk is driven by 34 risk loci (Fritsche et al., 2016); complement activation in AMD focuses on the outer blood/retinal barrier and not within the retinal tissue itself (Whitmore et al., 2015); BrM itself confers an immunological barrier and creates two distinct immunological landscapes within the eye (Clark et al., 2017); and the discovery of complement proteins, particularly the Factor H related proteins produced solely in the liver, may have disproportionate effects on complement turnover in specific organs, including the eye (Cipriani et al., 2020, 2021; Lorés-Motta et al., 2021).

5.2. Drug development in GA - targeting complement

The potential to target complement activation for the treatment of retinal disease has led to the formation of many new start-ups in this

A



B

Company	Asset	Target/Pathway	Indication(s)	Modality	Ph1 or Ph1/2	Ph2	Pivotal	Market	Deal / Partner
Roche/Novartis	Lucentis	VEGF-A	wet AMD/DME/DR/RVO	Antibody					
Regeneron/Bayer	Eylea	VEGF-A	wet AMD/DME/DR/RVO	Antibody					
Regeneron/Bayer	Eylea High-Dose	VEGF-A	wet AMD/DME/DR/RVO	Antibody					
Novartis	Beovu	VEGF-A	wet AMD/DME/DR/RVO	Antibody					ESBATech
Roche	Vabysmo	VEGF-A/Ang2	wet AMD/DME/DR/RVO	Antibody					
Roche	Susvimo	VEGF-A	wet AMD/DME/DR/RVO	Antibody					ForeSight Vision 4
Clearside	Xipere	Anti-inflammatory/ steroid	UME	Small molecule					Bausch/ US&CA right
Alimera	Iluvien	Fluocinolone	DME	Small molecule					
Abbvie	Ozurdex	Anti-inflammatory/ steroid	DME	Small molecule					
Regenx	RGX-314/subretinal	VEGF-A	wet AMD	AAV					Abbvie
Adverum	Ixo-vec	VEGF-A	wet AMD	AAV					
Outlook	Lytenava	VEGF-A	wet AMD/DME/DR/RVO	Antibody					
Opthea	OPT-302	VEGF-C/D	wet AMD	Antibody					Launch Therapeutics
Roche	RG6179	IL-6	DME	Antibody					
Unity	UBB2048	Tie2/VEGF	wet AMD/DME/DR/RVO	Antibody					
Oculis	OCS-01	Anti-inflammatory/ steroid	DME	Small molecule					
Ocuphire	APX3330	APE1/Ref-1	DR/DME	Small molecule					
OcuTerra	OTT166	Integrin inhibitor	DR	Small molecule					
Clearside	CLS-AX	Growth factor receptors/ TKI	wet AMD	Small molecule					
Ocular Tx	OTX-TKI	Growth factor receptors/ TKI	wet AMD/DME	Small molecule					
Oxular	OXU-001	Anti-inflammatory/ steroid	DME	Small molecule					
Ripple	IBE-814	Anti-inflammatory/ steroid	RVO/DME	Small molecule					Thea
Rezolute	RZ402	Plasma kallikrein	DME	Small molecule					
Unity	UBX1325	Bcl-xL	DME/wet AMD	Small molecule					
Ashvattha	D-4517.2	Growth factor receptors/ TKI	wet AMD	Small molecule/Dendrimer					
Ribomic	RBM-007	FGF-2	wet AMD	ASO					
Gene Signal	Aganirsen	IRS-1	wet AD/DME/RVO	ASO					
Sylentis	SYL1801	Nrarp	wet AMD	ASO					
RegenxBio	RGX-314/suprachoroidal	VEGF-A	wet AMD/DR	AAV					Abbvie
4DMT	4D-150	VEGF-A	wet AMD	AAV					
Exegenesis	EXG102-031	VEGF/Ang2	wet AMD	AAV					
Boehringer Ingelheim	BI764524	Semaphorin 3A	DR	Antibody					
Boehringer Ingelheim	BI765128	NRP1	DR	Antibody					
AskGene	ASKG712	VEGF-A/Ang2	wet AMD/DMA	Antibody					
Boehringer Ingelheim	BI836880	VEGF-A/Ang2	wet AMD	Antibody					
Clearside	Xipere	Anti-inflammatory/ steroid	DME	Small molecule					Arctic Vision/ Asian rights
Oculis	OCS-01	Anti-inflammatory/ steroid	CME	Small molecule					
Eyepoint	EYP-1901	Growth factor receptors/ TKI	wet AMD/NPDR/DME	Small molecule					
Exonate	EXN-407	VEGF-A	DME	Small molecule					J&J
PanOptica	PAN-90806	Growth factor receptors/ TKI	wet AMD	Small molecule					
AiViva	AIV007-E02	Growth factor receptors/ TKI	wet AMD	Small molecule					
Alcon	AR-14034	Growth factor receptors/ TKI	wet AMD	Small molecule					Aerie
Asclepix	AXT107	Tie-2	wet AMD/DME/DR/RVO	Peptide					
Ocugenix	OCU-10-C-110	CXCR3	wet AMD	Peptide					

Fig. 2. Clinical-stage programs for exudative retinal diseases. Visualization of all currently active clinical programs sorted by modality and stage. Mainly US and European private companies have been considered.

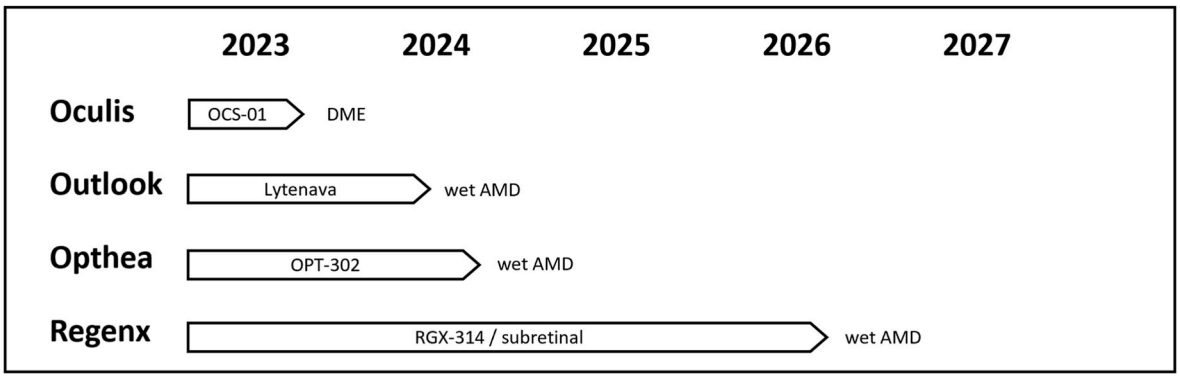


Fig. 3. Upcoming key pivotal read-outs in wet AMD and DME. The dates presented are based on information available on company websites and clinicaltrials.gov.

space over the last two decades, as well as a surge of interest in this mechanism from pharma. A schematic overview of the pathway and the different therapeutic approaches are illustrated in Fig. 5.

One of the first and most advanced complement-targeting agents in dry AMD/GA was an Ab fragment targeting factor D, called lampalizumab and developed by Roche/Genentech. In 2013, Roche/Genentech released encouraging data from the MAHALO study (NCT01229215), demonstrating that inhibition of the complement system by lampalizumab could be an effective way to slow down the disease progression of dry AMD/GA (Yaspan et al., 2017). The MAHALO study also suggested that a certain genetic variation in the complement protease complement factor I (FI) could serve as a prognostic marker for a positive treatment effect by lampalizumab, a precision medicine angle highly sought after in drug development. Lampalizumab was advanced into pivotal Phase 3 studies based on these data. The early results from MAHALO and the determination of Roche/Genentech to commit to an aggressive timeline for development, by moving lampalizumab directly into two large Phase 3 studies (CHROMA and SPECTRI, NCT02247479 and NCT02247531 respectively) further fuelled the complement space in dry AMD/GA and spurred the foundation and financing of multiple companies (e.g. Apellis, Iveric, Gyroscope, Gemini) targeting different proteins within the complement cascade (e.g. Complement component 3 (C3), Complement component 5 (C5), FI, FH) using various therapeutic modalities, including peptides, gene therapies, and aptamers. An overview of some of the companies is shown in Fig. 6. Unfortunately, only four years later, lampalizumab failed to show any meaningful effect on disease progression in dry AMD/GA, as evidenced by the results of both Phase 3 studies CHROMA and SPECTRI (Holz et al., 2018).

Despite this setback, there were reasons to believe that other modalities targeting the same or adjacent proteins in the complement cascade could still provide a positive treatment effect. In early 2023, Apellis Pharmaceuticals, the developer of pegcetocoplan (branded as Syfovre), received the first FDA approval for the treatment of dry AMD/GA (Apellis Pharmaceuticals, 2023). The approval came on the back of two Phase 3 studies (OAKS, NCT03525600, and DERBY, NCT03525613) and was further corroborated by a Phase 2 trial (FILLY, NCT02503332). Syfovre was tested in two dosing regimens, once monthly and every other month IVT. Depending on the regimen, it could show a slow-down of GA lesion area growth rate at month 24 of 18.1–21.9% and 17.4–18.1% in OAKS and DERBY, respectively (Apellis Pharmaceuticals, 2023c). Encouragingly, Syfovre's efficacy seems to increase with time on treatment. The ultimate administration frequency is indicated as every 25–60 days IVT as per Syfovre's FDA label (Apellis Pharmaceuticals, 2023c). While this approval represents a major clinical breakthrough, as the first drug ever to demonstrate an effect on disease progression in GA, this is a modest effect size. The treatment also has potential side effects that require careful consideration from physicians and patients. Syfovre treatment carries a 7–12% incidence of new CNV formation (Apellis Pharmaceuticals, 2023c), hypothesized to be induced by the polyethylene glycol moieties of the drug: polyethylene glycol induces a series of physiological changes like AMD (Lyzogubov et al., 2014) and was for a brief time a patented method of inducing CNV in mouse models of angiogenesis. This association has not gone unnoticed by the field, and none of the newer drugs currently in development adopt pegylation (except for Izervay, see below). In July and August 2023, Apellis reported seven cases of retinal vasculitis, for which the company could not yet establish a definitive root cause (Apellis Pharmaceuticals, 2023a, Apellis Pharmaceuticals, 2023c). At the time of this review, the most recent potential cause could be in the use of a specific 19-gauge filter needle which some injection kits contained. The company advised to use kits with an 18-gauge needle only. An extension study to evaluate the long-term safety and efficacy of pegcetocoplan continues to monitor patients who participated in OAKS and DERBY (GALE, NCT04770545) and is due to be completed in Q4 2025.

Another therapy, this time targeting C5 in the complement cascade, called avacincaptad pegol (branded as Izervay) has been developed by Iveric. Izervay was tested in only one dosing regimen, namely once monthly IVT and showed a slow-down of GA lesion area growth rate at month 12 of 18–35% in GATHER1 and GATHER2, respectively ((IVERIC bio, 2023); GATHER1, NCT02686658 and GATHER2, NCT04435366) (Khanani et al., 2023; Jaffe et al., 2021). Interestingly, a recent analysis by Paul Hahn, which was based on an anchored matched-adjusted indirect comparison between Izervay and Syfovre and presented at the ASRS 2023 (Crago and Hutton, 2023), indicates that monthly Syfovre showed a statistically significant 30% greater reduction in lesion growth rate compared to monthly Izervay. In contrast, there was no difference between every other month of Syfovre and monthly Izervay. (Khanani et al., 2023; Jaffe et al., 2021). Izervay is also pegylated and carries a similar risk of 7% for CNV formation (IVERIC bio, 2023). Driven by the size of this market and unmet medical needs, Astellas Pharma recently acquired Iveric for $5.9 B in Q2-2023. Izervay received approval from the FDA in August 2023 and is the second approved treatment option for dry AMD/GA patients. Fig. 6 below illustrates some of the major milestones in complement targeted treatments, culminating with the two approved drugs, Syfovre and Izervay.

5.3. *Clinical failures in complement modulation in GA*

While targeting the complement system has now achieved success in dry AMD/GA, with two approvals, it has been a long and challenging path. Numerous complement inhibitors have been through rigorous preclinical and clinical testing and failed. For example, eculizumab (traded as SOLIRIS by Alexion, part of AstraZeneca) is an FDA-approved therapy for atypical hemolytic uremic syndrome and paroxysmal nocturnal hemoglobinuria that targets the C5 protein in the complement system. In the Phase 2 COMPLETE trial (NCT00935883), the humanized

A

	Macugen	Avastin	Lucentis	Eylea	Beovu	Vabysmo	Eylea HD
Target	VEGF-A isoform 165	All VEGF-A isoforms	All VEGF-A isoforms	All VEGF-A, VEGF-B, PIGF isoforms	All VEGF-A isoforms	VEGF-A / ANG2	All VEGF-A, VEGF-B, PIGF isoforms
Modality	Aptamer	Full mAb	Fab fragment	VEGF trap	Single-chain antibody fragment	Bi-specific antibody	VEGF trap
Function	VEGF inhibitor	VEGF inhibitor	VEGF inhibitor	VEGF/PIGF inhibitor	VEGF inhibitor	VEGF and ANG2 inhibitor	VEGF/PIGF inhibitor
FDA-approval	2004	2004 (Colon cancer)	2006	2011	2019	2022	2023
FDA-approved indications	wAMD	No approval for ophthalmic use	wAMD/DME/ PDR/RVO/CNV	wAMD/DME/ DR/RVO/ ROP	wAMD/DME	wAMD/DME/ RVO	wAMD/DME/DR
Dosing frequency / Administration (wAMD)	Once every 6 weeks / IVT	3 monthly loading doses followed by extended injection intervals (pro re nata) / IVT	Monthly / IVT	3 monthly loading doses followed by every 8 weeks / IVT	3 monthly loading doses followed by every 8-12 weeks / IVT	3 monthly loading doses followed by extended injection intervals as determined by OCT & VA / IVT	3 monthly loading doses followed by every 8-16 weeks / IVT

B

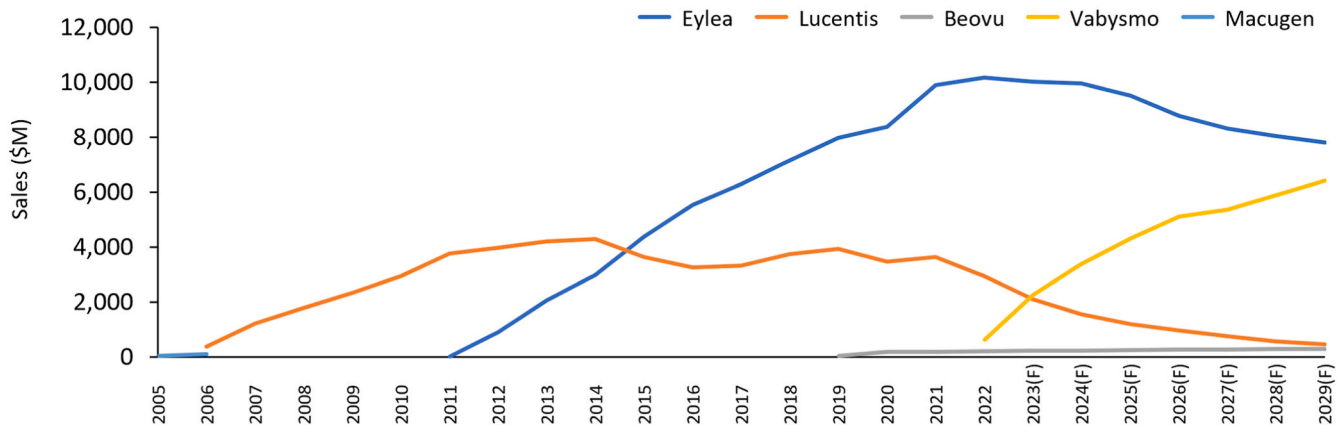


Fig. 4. Overview of approved anti-VEGF therapies. A) Table summarising the approved anti-VEGF therapies from 2004 until today. Dosing frequency and administration are only shown for wAMD and may vary for other approved indications; B) Annual sales and forecast of approved anti-VEGF therapies (Source: GlobalData). No disease-specific sales data for Avastin could be found, but sales in 2022 are estimated to be around $300 M.

monoclonal Ab was delivered by intravenous infusion in patients with dry AMD/GA (Yehoshua et al., 2014), but was shown to be ineffective.

Another prominent clinical failure was Gemini Therapeutics. Fuelled by several genetic studies, variants in the CFH gene were identified as one of the most risk-associated modifiers of disease and thus a promising drug candidate. The hypothesis was that a re-introduction of the wild-type form of FH protein in patients carrying CFH mutations could regain control of the complement system and prevent dry AMD/GA from progression. Gemini's recombinantly produced FH protein was administered by IVT injection monthly and reached Phase 2 trials (NCT04643886, NCT04684394). However, by 2017 it was acknowledged in the scientific field that complement-mediated pathogenesis of dry AMD/GA manifested on the systemic side of the outer blood-retinal barrier (Whitmore et al., 2015) and that FH would not be able to diffuse across BrM due to its size and level of glycosylation (Clark et al., 2017). Perhaps unsurprisingly, the Phase 2 trials failed to reach their endpoints, and further development was discontinued (Disc Medicine, 2022). By the end of 2022, Gemini Therapeutics was acquired in a reverse merger by Disc Medicine to pursue a pipeline outside of ophthalmology (Disc Medicine, 2022).

Similar to Roche/Genentech with lampalizumab, and Gemini with recombinant FH, other previous approaches focused on the delivery of established complement inhibitors into the eye itself by IVT injections (Rathi et al., 2023). Examples include LFG316 (Novartis), a monoclonal Ab against C5; CLG561 (Alcon/Novartis), a fully human Ab fragment against properdin (used both alone and in tandem with LFG316); and NGM621 (NGM Bio), a humanized monoclonal anti-C3 Ab. All of these, one way or another, failed to show efficacy in either Phase 2 or 3 trials. A more recent development is ANX007 (Annexon), a Fab fragment Ab therapy against C1q. A recent press release from Annexon revealed some

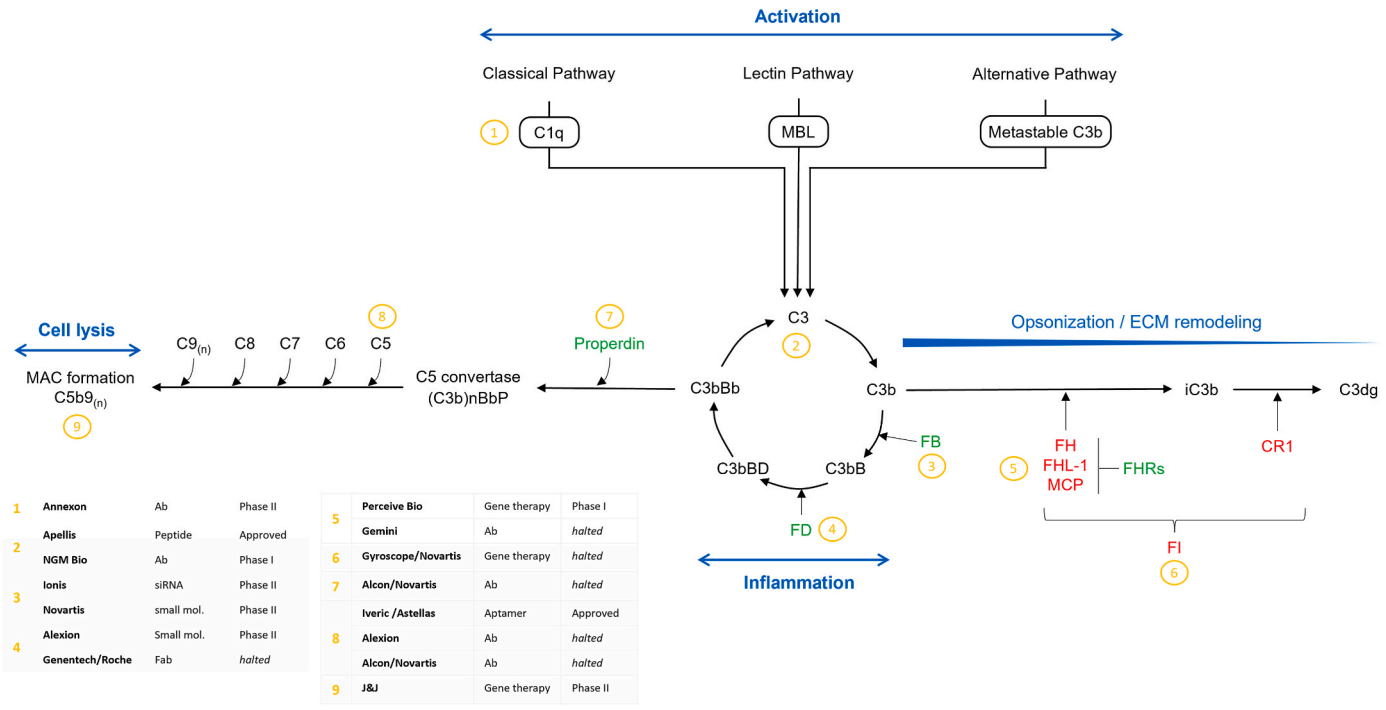


Fig. 5. Clinical targets within the complement cascade. Active and halted/discontinued clinical-stage & approved approaches are illustrated. Mainly US and European private companies have been considered.

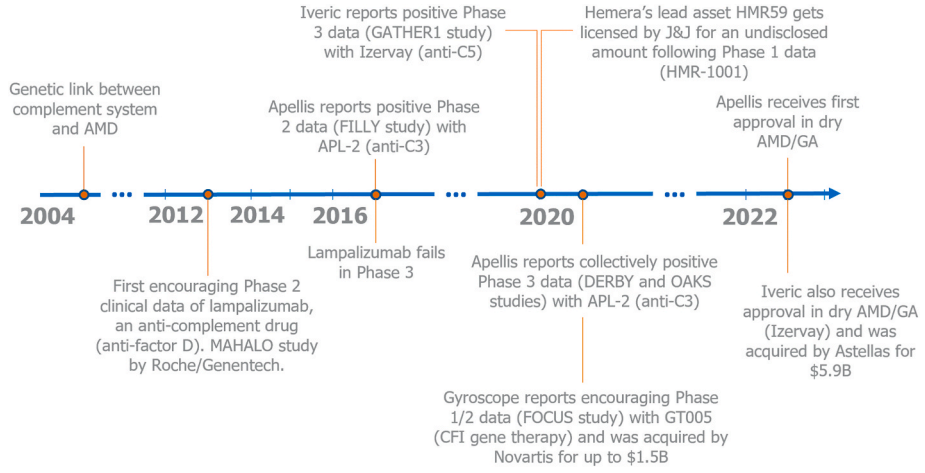


Fig. 6. Short history of AMD/GA drugs. Illustration of key milestones, positive and negative, on the way to the first approved drugs for dry AMD/GA in 2023.

top-line efficacy data from the ongoing Phase 2 ARCHER study (NCT04656561) (Annexon Biosciences Inc, 2023). It was confirmed that although by some measurements of BCVA there was a reduction in the risk of 15-letter loss in patients receiving the drug, no slowing in the progression of the GA lesion was observed, calling into question how well these BCVA measurements will translate in larger trials.

Ultimate answers as to why the above mentioned drugs failed are not available because, for example, correlations between drug pharmacokinetics and pharmacodynamics in ocular tissues are impossible to investigate given the invasiveness such an investigation would mean for patients. However, there is an interesting observation that can be stated for several unsuccessful trials that have involved IVT administered recombinant protein/Ab-based therapies: It is possible that Ab-based biochemistry simply does not allow for sufficient biodistribution to address the abundant complement targets. Beyond pure abundance, complement targets need to be addressed at the cell membrane, which means locally, rather than in a sink-effect-like fashion. Indeed, only a few of the next generations of complement targeting therapies in the ophthalmic space are still based on IVT administration of recombinant proteins (Rathi et al., 2023) and are attempting to deliver therapies designed with the eye's unique anatomical architecture in mind (de Jong et al., 2023). The recently announced failure of Gyroscope's gene therapy drug GT005 which we discuss in more detail below calls into question whether this is the key differentiating factor between IVT and e.g. subretinally administrated drugs in this therapeutic space (Novartis, 2023).

6. Gene therapy approaches in GA

A central challenge for dry AMD/GA therapies which only slow disease progression, but do not lead to vision gain as a positive reinforcement for patients to continue therapy, is the need for frequent

administrations. IVT injections every month or every other month are therefore difficult to explain and accept. A wave of next-generation complement-targeting therapies addresses this aspect by delivering the therapeutic protein via gene therapy, in theory providing a one-and-done treatment.

The most advanced approach is a gene therapy delivering the complement regulator FI, which is the protease responsible for inactivating the central protagonist of complement activation, the protein called C3b (Rathi et al., 2023), developed by Gyroscope Therapeutics, a biotech company founded in 2016, and financed initially by London-based biotech investment firm, Syncona. Gyroscope focused on emerging genetic data that defined a small cohort of patients whose circulating levels of FI are significantly lower than controls. Rare genetic variants in the complement factor I (CFI) gene leading to this phenotype are highly associated with AMD with extremely high penetrance (Hallam et al., 2020). A logical therapeutic intervention is to increase FI levels in patients who have low levels of endogenous FI. This was achieved by delivering extra copies of CFI by subretinal AAV2 gene therapy targeting the retinal pigment epithelium (RPE) cells in the retina (gene therapy candidate referred to as GT005). Positive Phase 1/2a results were obtained (FOCUS, NCT03846193) that demonstrated good safety and tolerability, as well as elevated FI levels and complement breakdown within the eye.

These data drove the acquisition of Gyroscope by Novartis for up to $1.5 Billion in 2022, including an upfront payment of $800 M. It was a landmark deal for the founding investor, Syncona, delivering an impressive ~$424 million upfront return. Other investors in Gyroscope, including Forbion, Sofinnova Investments, and T. Rowe Price Associates enjoyed a quick return following their investment into the company in 2021. Regrettably, Novartis has recently announced that further development of GT005 has been stopped. In a press release, Novartis states that “this decision was based on a recommendation from the independent Data Monitoring Committee following an overall risk-benefit assessment of available data from the program studies, which concluded futility criteria had been met. Importantly, no new safety signals were identified” (Novartis, 2023).

The news of Novartis abandoning GT005 remains too recent at the time of our review’s publication to have any true insight as to why the trials failed to show efficacy. Hypothetical reasons could include technical hurdles, such as inconsistent delivery of the AAV product via subretinal administration to large numbers of patients across multiple clinical sites, or biological limitations, indicating that delivering FI therapeutically might not translate into reduced GA lesion growth. Given the robust evidence, including two drug approvals in dry AMD/GA, that downregulating the activity of the complement system leads to reduced GA lesion growth, even when using different therapeutic modalities, we can only speculate that several different factors may have contributed.

Another clinical-stage gene therapy company targeting the complement cascade in dry AMD/GA is Hemera Biosciences. Hemera’s gene therapy delivers a soluble CD59 (sCD59) molecule, an inhibitor of the membrane attack complex (MAC) that is the final stage of complement activation, which helps promote inflammation and causes cell lysis (Menny et al., 2018). The observation of increased MAC deposition in the eyes of patients suffering from AMD (Mullins et al., 2014) prompted the hypothesis that this was a driver of the disease itself. Delivered by IVT injections of AAV serotype 2 (AAV2) gene therapy, this single administration drug is designed to protect retinal cells against complement-mediated MAC attack, despite the biochemical evidence showing that MAC deposition occurs in the choriocapillaris, just outside the outer blood-retinal barrier, and not within the retinal tissues itself (Whitmore et al., 2015; Chirco et al., 2016; Skei et al., 2010; Mullins et al., 2014). Nevertheless, in 2020 Hemera was acquired by J&J for an undisclosed amount (Johnson & Johnson, 2020), and subsequent results from a Phase 1 open-label dose escalation study (HMR-1001, NCT03144999) met the primary safety endpoints while showing a continued decline in GA lesion growth. Renamed JNJ-81201887, the sCD59 therapy has begun a Phase 2 trial (NCT05811351) with an expected study completion date of Q4-2025.

Several other biotech companies pursuing gene therapy approaches in the complement field are progressing toward trials in patients. Perceive Biotherapeutics seeks to address previous companies’ shortcomings by delivering the naturally occurring, truncated form of the FH protein (called factor H-like protein 1, or FHL-1), which is now known to predominate in the outer blood-retinal barrier in human eyes (Clark et al., 2014), primarily due to its ability to diffuse through BrM (Clark et al., 2017). The delivery modality is also modified, utilizing IVT delivered AAV-gene therapy to deliver the therapeutic payload in a single administration, thus avoiding the need for repeated injections. The Phase 1/2a trial using this gene therapy candidate (termed VOY-101) began recruiting patients in mid-2023 (NCT05380492).

Another biotech company, Ikarovec, is employing an AAV-based gene therapy approach to their treatments of ocular disease that combines the delivery of a soluble CD46, a complement inhibitor, and pigment epithelium-derived factor, which stabilizes newly formed blood vessels (Ikarovec). This preclinical program utilizes the latest AAV gene therapy technologies and attempts to address multiple aspects of different diseases in a single administered treatment. As such, although the primary indication is dry AMD/GA, the treatment candidate may also have benefits in wet AMD and DME.

Complement Therapeutics, a spin-out from the University of Manchester, is developing a gene therapy-delivered protein (CTx001) that acts as a potent co-factor for endogenous FI within the eye, and whose approach is more focused on complement modulation rather than inhibition (Complement Therapeutics). CTx001’s biodistribution profile and high-affinity target binding are believed to address the requirement for sufficient drugs to reach the ECM surrounding the choriocapillaris from within the eye by getting past the blood/retinal barrier. Similarly, the therapy also addresses the opsonization of tissues already undergoing complement over-activation by promoting disengagement of accumulated immune cells and can work in elevated levels of Factor H-related protein (FHR) proteins. Interestingly, Complement Therapeutics has undertaken a large non-interventional natural history study in AMD, where 250 patients are fully characterized for genetic risk, complementome profile, and disease progression (i-GAIN study, NCT05797896). It is hoped that patients for future clinical trials of CTx001 will benefit from this natural history study, by enabling stratification of the patient population for improved treatment benefit and a greater understanding of the effects of the intervention, depending on underlying patient characteristics.

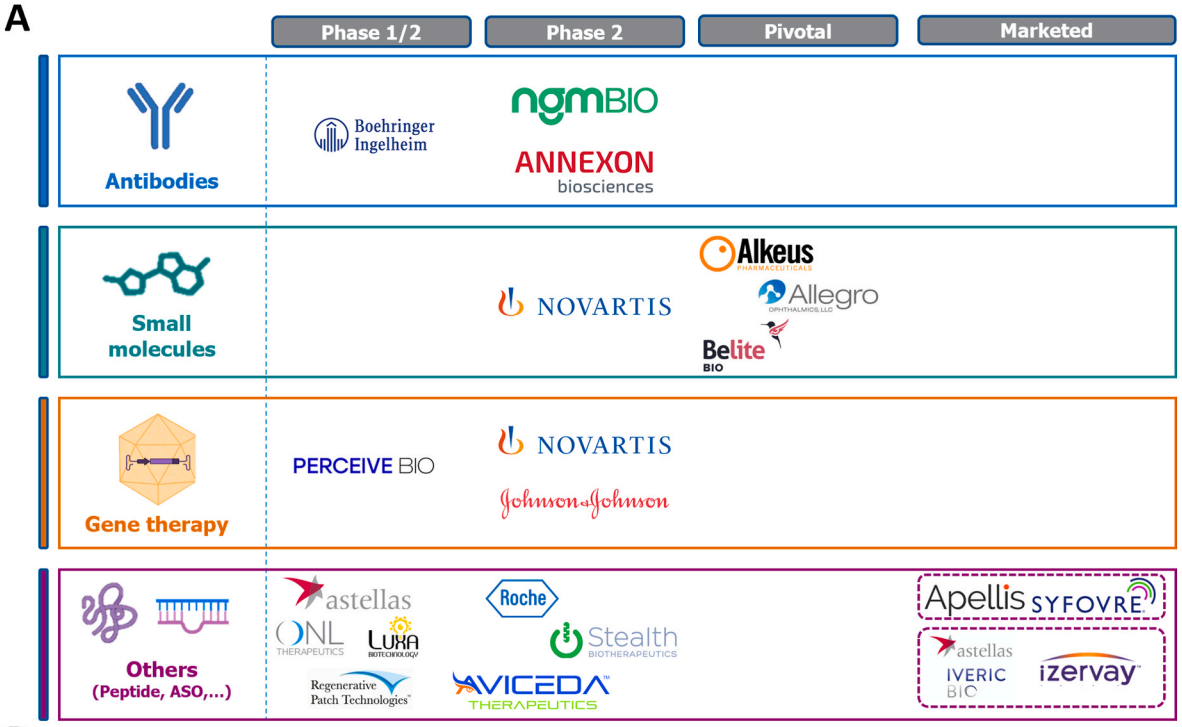
6.1. *Systemic approaches to complement modulation in GA*

In addition to one-time administered gene therapies, systemically administered complement targeting inhibitors, already approved or developed for indications outside ophthalmology, are also undergoing trials in dry AMD/GA. Alexion, a subsidiary of AstraZeneca, is testing their oral, anti-Factor D compound, danicopan, in Phase 2 trials (NCT05019521). Novartis has an oral, anti-Factor B compound, iptacopan, currently being tested in Phase 2 trials for early and intermediate dry AMD (NCT05230537). IONIS Pharmaceuticals, in partnership with Roche, is also targeting complement factor B, but is targeting its production in the patient’s liver, by delivering an anti-FB siRNA therapy by subcutaneous injection in a Phase 2 study (GOLDEN, NCT03815825). These therapeutic approaches aim to reduce systemic levels of complement proteins, and differ from the targeted, organ-specific approaches described in the previous section, presumably motivated by the recent findings that complement proteins are expressed locally in the choroid and endothelium of the choriocapillaris (Demirs et al., 2021; Zauhar et al., 2022). We await the outcome of these trials to determine if systemic reduction of complement can deliver sufficiently effective modification of complement turnover in the back of the eye.

6.2. Looking ahead – what's beyond complement in GA?

While the first successes with complement-targeting drugs can be seen as tremendous progress, for patients, their families, drug makers, and regulators, these drugs have an inherent limit of what they can physiologically achieve. At the most, they could stop disease progression and even that seems far from realistically achievable. To date, the best clinical results have shown up to ~17–35% deceleration of disease

A



B

Company	Asset	Target/Pathway	Modality	Ph1 or Ph1/2	Ph2	Pivotal	Market	Deal / Partner
Apellis	Syvovre	C3/complement	Peptide					
Astellas	Izervay	C5/complement	Aptamer					Iveric
Alkeus	ALK-001	Visual cycle	Deuterated VitA					
Allegro	Luminate	Integrin receptor	Small molecule					Bausch & Lomb
Belite	Tinlarebant	RBP4 inhibitor	Small molecule					
Novartis	PPY988	FI/complement	AAV					Gyroscope
J&J	JNJ-1887	CD59/complement	AAV					Hemera
NGM	NGM621	C3/complement	Antibody					MSD
Annexon	ANX007	C1q/complement	Antibody					
Novartis	LNP023	FB/complement	Small molecule					
Alexion/AZ	ALXN2040	FD/complement	Small molecule					
Roche	RG6299	FB/complement	ASO					Ionis
Stealth	Elamipretide	Cardiolipin/oxidative stress	Peptide					
Roche	RG6501	RPE cells	Cell therapy					Lineage
Aviceda	AVD-104	Complement	Glycomimetic nanoparticle					
Galimedix	GAL-101	Aβ	Small molecule					
Perceive	VOY-101	Complement	AAV					
Boehringer Ingelheim	BI 771716	C3/complement	Antibody					CDR Life
Astellas	ASP7317	RPE cells	Cell therapy					Ocata
Reg Patch Tech	CBCP-RPE1	RPE cells	Cell therapy					
ONL	ONL1204	FasR inhibitor	Peptide					
Luxa	RPESC-RPE-4W	RPE cells	Cell therapy					

Fig. 7. Clinical-stage programs for dry AMD/GA. Visualization of all currently active clinical programs sorted by modality and stage. Mainly US and European private companies have been considered.

progression (Apellis Pharmaceuticals, 2023c; IVERIC bio, 2023). Beyond the effect size itself, it would be beneficial to develop drugs that are more convenient to administer, e.g. oral or much less frequently injected, and which would allow earlier intervention during the natural course of the disease. As of today, most dry AMD treatments are positioned for the late-stage form GA. However, there is a large unmet need in intermediate AMD, where patients would unlikely accept frequent IVT injections. Current hurdles for such development are amongst others safety of systemic drugs, validation of new biological targets, selection of patients where clinical benefits can be demonstrated in a realistic time period in a clinical study, and regulatory flexibility for new and/or modified endpoints. As far as efficacy is concerned, the holy grail remains the restoration of the lost retina and consequently a gain of vision. Given that photoreceptor and RPE cells are considered post-mitotic cells (Eckmiller, 2004), truly regenerative approaches need to be applied to achieve any vision gain. We identify at least three additional pillars of therapeutic approaches covering various modalities: (1) Cell therapy; (2) Optogenetics; and (3) alternative targets outside of complement such as targeting the visual cycle.

Currently active, clinical-stage programs targeting dry AMD/GA are summarized in Fig. 7.

6.3. Cell therapy

One approach is to replenish missing RPE cells by either injecting or implanting exogenously grown RPE cells (Sharma et al., 2020). These cells are typically derived from embryonic or induced pluripotent stem cells and are either used in a cell suspension or immobilized on a scaffold. While the idea is extremely elegant and technologically exciting, the idea has been around for more than a decade but so far has failed to deliver major positive clinical results. We speculate around some of the anticipated challenges: (1) Where to place these cells to still rescue residual photoreceptors? (2) Why should these RPE cells survive while the endogenous RPE cells die? (3) How to show reliable vision gains and overcome interpatient variability, also related to the procedure, and so on. Lineage Therapeutics seems to be the most advanced (Phase 1/2a) and could secure a deal with Roche/Genentech in 2021 ($50 M upfront + $620 M in deferred milestones). While this partnership is a positive outcome that allows the technology to be further developed, it is not a deal that would qualify as an attractive exit for most investors. This case exemplifies the struggle of this particular field: innovative technology with a big promise that needs a lot of capital to generate data but little progress over the last decade, and accordingly limited interest by pharma as reflected by low deal volumes.

6.4. Optogenetics

Another approach to restoring vision is optogenetics. The basic idea is to compensate for the absence of light-sensing photoreceptors by transducing other retinal cells, like bipolar or retinal ganglion cells, with a channel rhodopsin molecule to make them “pseudo-photoreceptors” (McGregor et al., 2020) and enable alternative, healthy cells in the retina to take over the light-sensing role of the photoreceptors lost in GA. Numerous companies have emerged with nuanced differences in the choice of their sensor rhodopsin molecule, subtly altering its light spectrum, sensitivity, and kinetics. The outcome so far is too early to be judged, although some partial success was recently seen in blind patients suffering from retinitis pigmentosa (RP) in the PIONEER study (NCT03326336) (Sahel et al., 2021). It is still unknown how bipolar and/or ganglion cells can process a light stimulus into a meaningful temporally and spatially resolved signal that can be further processed by the visual cortex and turned into a high- or at least medium-resolution image. Anecdotal reports suggest that current clinical optogenetic approaches that already have clinical data rather create confusion for the patients because the parameters mentioned above cannot be achieved and patients see distorted pictures, delayed movements, etc. Companies in active development include Ray Therapeutics, Nanoscope, GenSight, and Arctos (acquired by Novartis in 2021 for an undisclosed amount).

6.5. Visual cycle modulators

Finally, there are attempts to address the disease by targeting alternative mechanisms, such as the visual cycle. The yin & yang of the visual cycle is that it is required to function properly to regenerate 11-cis-retinal and at the same time, the same process if affected by a mutation or another malfunction, can create excessive amounts of toxic cell waste. This waste, often represented by the terms A2E and/or lipofuscin, creates oxidative stress which initially “clogs” RPE cells and ultimately kills them irreversibly (Feldman et al., 2022). Hypothetically, slowing down the visual cycle should result in slower disease progression if this is the mechanism of primary cell death. The connection of this mechanism to disease biology was initially made for Stargardt disease rather than for dry AMD/GA. The application of the same mechanism to dry AMD/GA was likely made due to comparable fundus autofluorescence findings in the junctional zone surrounding the atrophy in both diseases (Schmitz-Valckenberg et al., 2008). However, companies like Acucela could not convincingly demonstrate that and had to declare failure in 2016 with its drug emixustat. Emixustat is primarily an RPE65 isomerase inhibitor which effectively slows down the regeneration of 11-cis--retinal, thereby reducing the rate of the visual cycle and the accompanied buildup of toxic waste products, such as A2E and lipofuscin (Zhang et al., 2015). Despite encouraging target engagement data (delayed dark adaptation is an expected side effect and was used as a biomarker) there was no significant effect on GA lesion growth progression after two years of treatment. The company, now operating under the name of Kubota, conducted a follow-on Phase 3 study with emixustat in Stargardt disease (NCT03772665), again failing to show efficacy (Kubota Vision, 2018). Another company in this space is Katairo targeting the removal of lipofuscin using a small molecule belonging to the tetrahydropyridoether class of compounds, (originally called soraprazan but now renamed remofuscin) (Julien-Schraermeyer et al., 2020). However, no clinical efficacy data have yet been disclosed for their AMD trials in Stargardt disease (STGD).

There are at least two companies still actively developing drugs targeting the visual cycle: Belite Bio and Alkeus. Belite Bio is testing an oral RBP4 small molecule inhibitor intending to reduce ocular vitamin An uptake from the circulation (Belite Bio). The company is currently in two Phase 3 studies for dry AMD/GA and Stargardt (Phoenix and Dragon; NCT05949593 and NCT05244304). Alkeus on the other hand has focused its efforts on Stargardt initially and in November 2023 announced positive data from its Phase 2 study (TEASE-1; NCT04239625). The drug ALK-001, which is a deuterated form of vitamin A and somewhat similar to Belite’s drug reduces ocular vitamin A concentrations and demonstrated a 21% slowing in the growth rate of atrophic retinal lesions compared to the untreated arm (Alkeus Pharmaceuticals, 2023). The company is currently conducting two further studies with the same drug, one Phase 3 in dry AMD/GA (SAGA; NCT03845582) and one Phase 2 in Stargardt (TEASE-2; NCT02402660).

6.6. Promising clinical pipeline in GA

While it took a relatively long time to establish and bring the first successful product to the market in dry AMD/GA, the currently rich preclinical and clinical pipeline is encouraging and holds significant promise for more drugs to succeed. More than ten programs are in late-stage clinical development, again with a broad spectrum of modalities. Looking at drug mechanisms, it is no surprise that complement-targeting approaches are dominating given that this is the only clinically validated pathway so far. However, there is still a lot of room for improvement, be it administration frequency, effect size, or safety. Both biotech and large Pharma companies pursue the same goal in partnerships and on a standalone basis, although consolidation of promising retinal programs,

including exudative programs, is expected to happen upon more clinical data. Key, potentially pivotal read-outs, and possibly new lessons are expected soon from at least five programs (Fig. 8).

7. Innovation in the treatment of inherited retinal disease

Inherited retinal degeneration (IRDs) is a heterogeneous group of diseases characterized by a causative genetic link and unfortunately, in all cases but one, by lack of available therapies. For the sake of simplicity, this review covers the two largest groups of IRDs, namely STGD and RP. Given the inherited nature of these diseases, the field is dominated by two advanced modalities: gene therapy, especially when looking at the clinical stage companies (Fig. 9), and gene editing (Table 2).

7.1. Gene therapy in IRD

The first ocular-specific gene therapy was approved by the FDA in 2017 for treating a form of RP called Leber congenital amaurosis 2 (LCA2). LCA2 is a rare inherited retinal disease that causes progressive blindness and is usually diagnosed at birth or the first few months of life (Perrault et al., 1999). There are nineteen different forms of LCA, one of which is referred to as biallelic RPE65-mediated LCA, or LCA2, and it is this subtype that is treated with voretigene neparvovec (Luxturna) (Maguire et al., 2021). Originally developed by Spark Therapeutics, Luxturna uses AAV2 gene therapy, delivered by subretinal injection, to deliver new copies of the RPE65 gene into the RPE cells at the back of these children's eyes. The gene therapy is not a complete cure for the condition but substantially improves vision in treated patients. Spark Therapeutics initially partnered the ex-US rights for Luxturna with Novartis in 2018 in a $170 million deal. Subsequently, Spark was acquired by Roche in December 2019 for $4.8 billion, marking one of the largest biotech deals in the retinal therapeutics field (Spark Therapeutics, 2019; Novartis, 2018) (Table 1).

Luxturna marks a major milestone in the history of ophthalmic drug development, being the first approved gene therapy for a retinal disorder. Luxturna is also remarkable for its regulatory journey, by successfully navigating development for a disease without any regulatory precedent for clinical endpoints to support approval, and by doing so creating a de novo regulatory path. The team at Spark was able to agree with the FDA on a new endpoint, which was the mean bilateral, multiluminance mobility testing score change: in simpler terms the ability of a patient to navigate through a course of obstacles under varying lighting conditions.

The acquisition of Spark Therapeutics by Roche was an important endorsement of the commercial attractiveness to invest in advanced therapies in rare diseases in ophthalmology, although the acquisition price was likely not exclusively driven by Luxturna, given the small patient population, but also by Spark's pipeline in and outside ophthalmology, and the broader technology platform. However, market data today shows that Luxturna did not deliver commercially and so far, lags far behind projected sales expectations. At the time of the acquisition, consensus sales forecast was around 350–400 million USD worldwide sales. Luxturna today delivers significantly below $100 million to Roche (US rights) & Novartis (ex-US rights) (Evaluate; GlobalData). This disappointing market performance of Luxturna has at least three potential explanations: (1) Patients need to be identified through genetic screening and an assessment of residual viable retinal cells by optical coherence tomography (OCT). These assessments can often only be performed by specialized treatment centers, requiring patients to travel long distances which creates the first barrier; (2) The treatment can only be handled at specialized sites, due to the presentation of the drug product, i.e. −65 °C frozen viral drug, and the administration procedure, i.e. subretinal injection; (3) The drug price for Luxturna in the US is $425,000 per eye (approx. 30% less in Europe), which has generated renewed discussion of reimbursement schemes and sustainability of new treatments at such a price, despite being a single administration.

In summary, despite the commercial challenges of Luxturna, its approval, and Spark's pioneering approach created a wave of confidence for other biotech and pharma companies to develop AAV-based drugs in IRDs. To date, a long list of companies has developed differentiated and scientifically innovative AAV-based drugs for the various forms of RP (Fig. 9).

7.2. Cell therapy in IRD

Another approach to restoring vision in RP has been cell therapy. For several years, the two most prominent companies in this space have been jCyte (jCyte) and ReNeuron (ReNeuron). Both companies utilize similar cell products that are derived from fetal, retinal progenitor cells with the major difference being that jCyte injects those cells IVT intending to achieve a protective effect on photoreceptors by a secreted cocktail of neurotrophic factors, whereas ReNeuron positioned themselves as a truly regenerative approach by injecting the cells subretinally to achieve integration into tissue and differentiation towards new photoreceptors. Over several years, jCyte generated encouraging clinical results showing preservation and even gain of vision in some RP patients, however, the company has not disclosed much clinical progress since 2020 after publishing Phase 2 b results. ReNeuron has completely stopped its efforts in RP. Although initial Phase 2 data from seven patients looked promising, showing close to two lines of vision gain at one year, the effect waned thereafter, and the company decided to

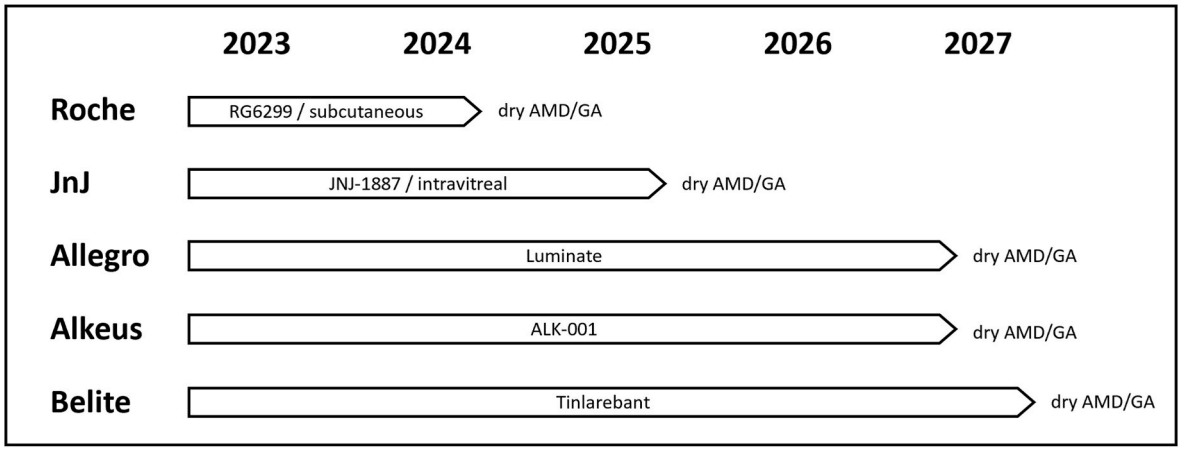
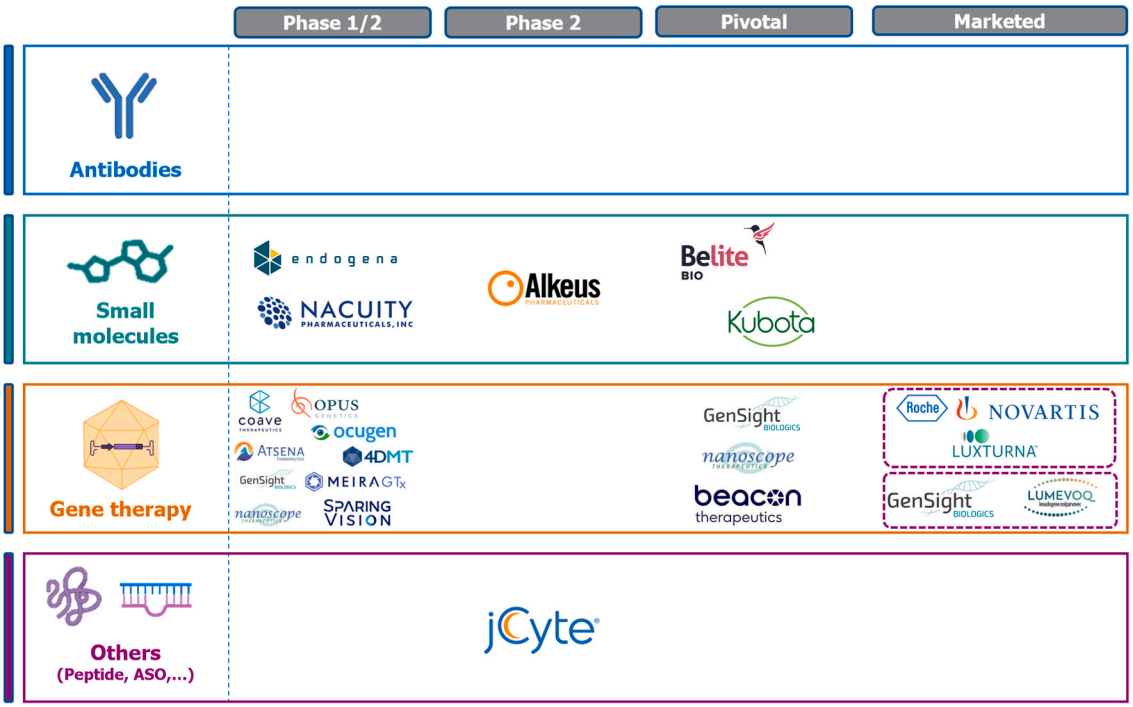


Fig. 8. Upcoming key pivotal read-outs in dry AMD/GA. Date presented is based on information available on company websites and clinicaltrials.gov. Not all studies have started yet but might be in planning.

A



B

Company	Asset	Target/Pathway	Indication(s)	Modality	Ph1 or Ph1/2	Ph2	Pivotal	Market	Deal / Partner
Roche/Novartis	Luxturna	Gene correction	LCA2	AAV					Spark Tx
GenSight	GS010 (US)/ Lumevoq (EU)	Gene correction	LHON	AAV				*	
Nanoscope	MCO-010	Optogenetic therapy	RP	AAV					
Beacon	AGTC-501	Gene correction	XLRP	AAV					
Belite	Tinlarebant	RBP4 inhibitor	STGD1	Small molecule					Lin Bio
Kubota	Emixustat	Visual Cycle	STGD2	Small molecule					
Alkeus	ALK-001	Visual Cycle / VitA	STGD1	Small molecule					
jCyte	jCell	Neurotrophic cell therapy	RP	Cell therapy					Santen
Coave	CTx-PDE6b	Gene correction	RP	AAV					Thea
Atsena	ATSN-101	Gene correction	LCA1	AAV					
Atsena	ATSN-201	Gene correction	XLRS	AAV					
Opus	OPGx-LCA5	Gene correction	LCA5	AAV					
Sparing Vision	SPVN06	Protection of cones metabolism	RP	AAV					
GenSight	GS030	Optogenetic therapy	RP	AAV					
Ocugen	OCU400	Gene correction	RP/LCA10	AAV					
Nanoscope	MCO-010	Optogenetic therapy	STGDT1	AAV					
Meira GTx	AAV-RPGR	Gene correction	XLRP	AAV					J&J
Meira GTx	AAV-RPE65	Gene correction	LCA2	AAV					
Meira GTx	AAV-CNGA3	Gene correction	Achromatopsia	AAV					J&J
Meira GTx	AAV-CNGB3	Gene correction	Achromatopsia	AAV					J&J
4DMT	4D-125	Gene correction	XLRP	AAV					
4DMT	4D-110	Gene correction	Choroideremia	AAV					
Kiora	KIO-301	Optogenetic therapy	RP	AAV					
Nacuity	NP-1	Oxidative stress	Usher	Small molecule					
Endogena	EA-2353	Regeneration of photoreceptors	RP	Small molecule					

Fig. 9. Clinical-stage programs for IRDs. Visualization of all clinical-stage programs sorted by modality and stage. * indicates that additional studies, besides the most advanced, are ongoing. Mainly US and European private companies have been considered.

Table 2
List of gene-editing companies with (publicly disclosed) retinal therapeutics programs in preclinical development.

Company	Program	Modality	Delivery	Indication
Emendo	EMD-201	Cas (OMNI)	unknown	RP
Emendo	EMD-202	Cas (OMNI)	unknown	Cone-rod dystrophy
Emendo	EMD-203	Cas (OMNI)	unknown	Macular dystrophy
Prime	RP/Rhodopsin	Prime Editor	AAV	RP/Rhodopsin
Prime	RP/Usher Syndrome	Prime Editor	AAV	RP/Usher Syndrome
SalioGen	Stargardt disease candidate	Saliogase	LNP-base	Stargardt disease
SalioGen	Usher Disease candidate	Saliogase	LNP-base	Usher syndrome
SalioGen	RP1 candidate	Saliogase	LNP-base	RP1
SalioGen	RP25 candidate	Saliogase	LNP-base	RP25
SparingVision (w/ Intellia)	SPVN50	Cas9	unknown	Undisclosed
SparingVision (w/ Intellia)	SPVN60	Cas9	unknown	Undisclosed
SparingVision (w/ Intellia)	SPVN70	Cas9	unknown	Undisclosed
Spotlight	Ocular candidate	TAGE	Other	Undisclosed

discontinue the program in RP.

7.3. Multiple modalities to treat stargardt disease

STGD is the largest IRD in terms of prevalence and in contrast to RP where retinal degeneration starts in the periphery and progresses towards the center encroaching the macula and the fovea, STGD affects the macula, therefore affecting central vision early on during the disease course, as previously discussed in many reviews (Fujinami et al., 2023). While some peripheral vision is usually maintained, central vision is lost (Macular Society, 2021). The most common form of STGD is the so-called STGD1 which is caused by mutations in the ATP-binding cassette transporter 4 (ABCA4) gene, coding for an ATP-binding cassette transporter in the outer segments of photoreceptors (Allikmets et al., 1997; Heath Jeffery et al., 2021). The lack of functional ABCA4 leads to the accumulation of oxidative toxic waste products, such as A2E and lipofuscin, as described before. Given its biological linearity, it is not a surprise that the most prominent therapeutic approach in STGD1 is a corrective gene therapy for ABCA4. The challenge in this approach is the size of the ABCA4 gene (6.8 kb) which is too large for the capacity of a normal AAV (typically up to 4.7 kb). Several companies have developed strategies to circumvent this issue by delivering the gene in two fragments, e.g. AAVantgarde Bio (AAVantgarde Bio), Splice Bio (SpliceBio), ViGeneron (ViGeneron), or by using truncated versions of the protein to reduce the size, e.g. Astellas/Iveric (Iveric Bio), or by leveraging gene editing to repair the gene, e.g. Abeona (Abeona Therapeutics) and Ascidian (Ascidian Therapeutics). There are also non-gene therapy-related approaches in STGD1 which include targeting the visual cycle similar to the idea in dry AMD/GA by companies like Belite Bio (as discussed above), or Stargazer (NCT04489511; program completed and discontinued (Stargazer Pharmaceuticals, 2020)), RPE cell therapy such as one by Astellas through their acquisition of Ocata in 2016 (progress of the program has been unclear for many years), or alternative mechanisms of action, such as the lipofuscin removal approach by Katairo (as discussed above) or optogenetic therapy by Nanoscope (Nanoscope Therapeutics).

7.4. Next generation: genome editing

Genome editing technologies are a powerful tool to treat a wide variety of diseases, including both genetic and non-genetic ocular diseases. A landmark paper in 2012, by the laboratories of the Nobel prize laureates Emmanuel Charpentier and Jennifer Doudna, described that CRISPR-Cas nucleases can be programmed with RNA for targeted gene disruption (Jinek et al., 2012). Shortly after, Le Cong et al. demonstrated for the first time that the CRISPR/Cas system can also be used for precise cleavage of endogenous genomic loci in the mammalian genome (Cong et al., 2013). The first generation of CRISPR/Cas9 systems are, however, poorly suited for precise correcting mutations in most cases. Luckily, these discoveries were only the start of the new area of genome editing, and recently additional gene editing agents, including base-editors and prime-editors were described that enable precise gene corrections (Komor et al., 2016; Anzalone et al., 2019; Anzalone et al., 2020). The eye is a particularly interesting organ for gene editing given its contained anatomy and immune-privileged nature. There are several active genome editing programs for ocular indications in preclinical development (Table 2), with likely more gene editing companies working on retinal programs that have not yet been publicly disclosed. Only EDIT-101, developed by Editas Medicines for the therapy of LCA type 10 (LCA10), has progressed into patients today (NCT03872470). The program meanwhile was discontinued, despite demonstrating encouraging preliminary efficacy signals of consistent improvement in BCVA (Editas Medicine, 2022; Maeder et al., 2019). Regardless of the discontinuation, the study provides the first clinical proof-of-concept that CRISPR-based gene editors can be delivered safely to the eye and can potentially provide a promising alternative treatment modality to “cure” IRDs. However, today’s editing tools and partly delivery vehicles are not yet ideally suited to cover the broad range of corrections that it would require to “cure” IRDs. Knocking down a mutated gene by CRISPR or correcting short stretches of DNA by base- and prime-editing, are sophisticated and promising first-generation approaches. Prime Medicine recently presented its first in vivo data demonstrating that prime-editing can correct mutations accounting for approximately 60% of patients with RHO adRP with up to 70% precise correction of the RHO p-P23H mutation and up to 65% of the RHO p. v345 L and p. P347L mutation in a humanized mouse model, using a dual-AAV delivery system (Prime Medicine, 2023). Building on the evolution of gene editing tools, we expect the next wave of gene editing strategies to leverage the full spectrum of possible edits, including excision, insertion, inversion, and exchange, for small and large DNA stretches. This type of breadth will unlikely be possible with tools like nucleases but rather requires the use of a highly versatile class of editing enzymes. Seamless Therapeutics, while not having announced any programs in ophthalmology yet, is developing evolved designer recombinases that could fulfill this promise. In totality, gene-editing tools are a modality that could revolutionize the treatment of IRDs, and the field should be monitored closely.

8. Investment landscape in retinal diseases

Establishing new disease models, exploring possible preclinical and clinical endpoints, and understanding distinct patient populations, are all critical elements of the long journey to discover and develop new therapies for retinal diseases. To facilitate researchers to experiment, significant funding for early and late-stage biotech companies is required. And there is good news: over the last two decades, the number of investments per year in companies with retinal programs has increased about threefold (Fig. 10A). Investment is not limited to early ideas financed by relatively modest funding rounds, but increasingly clinical-stage programs can be developed by biotech companies on a standalone basis, with increasingly larger financing rounds. Between 2004 and today, the average financing round has almost quadrupled from around $17 M in 2004 to around $63 M in 2022 and 2023 (Fig. 10B). In our Top 15 ranking, Series B and Series C financing rounds

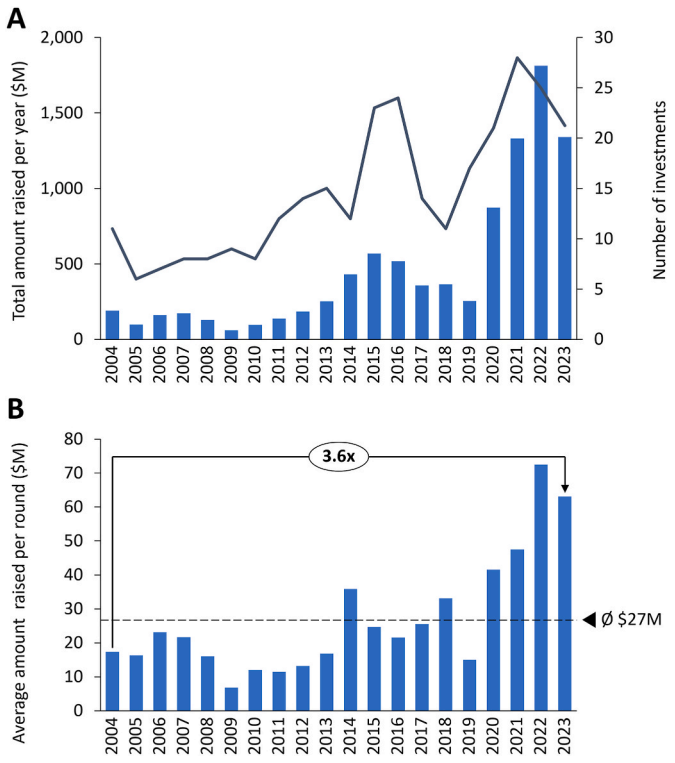


Fig. 10. Trends in VC investments in retinal therapeutics from 2004 until today. A) Total amount of VC investments made in retinal therapeutics companies per year in million dollars and the number of investments made per year. 2023 values are annualized. Bar graph shows the total amount raised per year ($M) (left y-axis) and the line graph shows the number of investments per year (right y-axis). B) Bar graph showing the average financing round size per year. The dotted line represents the average amount raised across the visualized time interval and the arrow shows the fold increase of the average financing round size comparing 2004 with 2023. US and European private companies, with at least one retinal pipeline program, have been considered. Technology platform companies (e.g. delivery or new modality platforms, etc.) have been excluded. A total of 294 financing rounds have been considered.

reached levels up to $150 million (Table 3). This is a testament to (1) positive progress in drug development and (2) the continued belief and support of VC investors in ophthalmology. This trend is particularly important in light of the still numerous late-stage clinical failures after a biotech company has been acquired by Pharma. The likelihood of drug approval for ophthalmic drugs after a positive Phase 2 read-out is ~47% only and compares unfavorably to several other therapeutic areas ((BIO, QLS Advisors, Informa UK Ltd, 2021); this number includes all ophthalmic indications, not only retinal diseases). The availability of larger funds provided by VCs to run larger Phase 2 b and/or even pivotal Phase 3 studies will allow us to close this potential gap of innovation in the coming future.

The positive trend also follows an overall growing biotech market, not specifically related to ophthalmology, but nevertheless provides the necessary means to support innovation in ophthalmology and reflects a growing interest of investors over this period. It's clear that the field is moving decisively to gene therapy as the leading technology in retinal disease: 9 out of the 15 largest financings were for gene therapy companies, which is also evidenced by the interest of pharma to acquire assets from biotech companies, with 7 out of 10 of the largest transactions (Table 1) covering advanced therapeutics. With a growing interest in ophthalmology from VC, and larger financing rounds being consummated, the field is well positioned to conduct meaningful clinical trials to investigate new treatments.

9. Conclusions

The past two decades have witnessed a remarkable evolution in retinal therapeutics, highly driven by groundbreaking advancements in therapeutic interventions. In this paper, we have reviewed the progress across three main therapeutic areas: From the initial milestone of anti-VEGF therapy, started by the landmark approval of Macugen in 2004, over the approval of Luxturna, the first ocular-specific gene therapy in 2017 for the treatment of LCA2, to the recent approvals of Apellis' and Iveric's drugs for dry AMD/GA. These successes in the first place generate great hope for millions of patients suffering from retinal diseases but also capture the attention of VC investors, who have invested close to $10 billion into research and development in this period. While the average financing round size was $63 million for the period between 2004 and today, many of the larger investments reaching over $100 million per financing round were closed in the last few years, indicating an upward trend. This has raised the profile of biotech innovation in retinal therapeutics to mirror other more established areas in biotech, such as oncology or rare diseases. The surge of investment has been paralleled by a growing appetite from pharma in the ophthalmology sector, highlighted by the most recent mega-deal, the acquisition of Iveric by Astellas for $5.9 billion. Pharma companies have become aware of the enormous impact and financial success they can generate, as showcased by blockbuster anti-VEGF drugs, such as Lucentis and Eylea. With scientific and clinical breakthroughs across all three disease areas, larger investments and exits are likely to continue in the future, further expanding the field of retinal therapeutics as an attractive area for investment and delivering innovation to patients.

Looking ahead, there is a rich pipeline of advanced clinical programs

Table 3
Summary of the 15 largest financings of retinal therapeutics companies since 2004
US and European private companies, with at least one retinal pipeline program, have been considered. The table has been sorted by round size.

Company	Year	Financing round	Round size in $ million	Target/Pathway	Modality
Frontera	2022	Series B	160	undisclosed	AAV gene therapy
Unity	2017	Series B	151	Bcl-xL/Tie2/VEGF Inhibition	Antibody/Small molecule
Alkeus	2023	Series B	150	Visual cycle modulator	Small molecule
Gyroscope	2021	Series C	148	FI/complement	AAV gene therapy
Unity	2016	Series C	116	Bcl-xL/Tie2/VEGF Inhibition	Antibody/Small molecule
Ray Therapeutics	2023	Series A	100	Optogenetics	AAV gene therapy
Annexon	2020	Series C	100	C1q/complement	Antibody
4DMT	2018	Series B	90	Multiple	AAV gene therapy
Iveric	2013	Series C	83	C5/complement	Aptamer
Life	2022	Series C	82	Epigenetic reprogramming and autophagy	AAV gene therapy
Complement Tx	2023	Series A	79	CR1/complement	AAV gene therapy
Perceive	2023	Series B	78	Undisclosed/complement	AAV gene therapy
Vedere Bio II	2021	Series A	77	Optogenetics	AAV gene therapy
Sparing Vision	2022	Series B	76	Cone function and protection	AAV gene therapy/gene editing
Intergalactic	2021	Series A	75	Abca4 correction	Non-viral gene therapy

for exudative retinal diseases, dry AMD/GA, and IRDs, which are expected to deliver pivotal read-outs of clinical data in the coming years. Akin to what we have seen in wet AMD, we expect the first approvals in dry AMD to be followed by combination approaches to improve the overall treatment effect. Combining orthogonal, potentially synergistic, or at least additive mechanisms, such as modulation of the complement system and oxidation, lipid metabolism, and neuroprotection, seem plausible.

Gene therapy holds great promise to offer new and enhanced treatment options for patients with retinal disease, and is being applied in multiple, innovative ways: as a bio-factory, using AAV to deliver a VEGF-inhibitor, and reducing or eliminate the need for frequent injections; as protein replacement, to correct the function of a mutated disease-causing gene, or to convey new biological function to healthy cells to replace cells lost to disease using optogenetics. In some cases, combinations of several different modalities may become possible in the future, for example, a one-time AAV gene therapy, combined with a small molecule therapy to further improve treatment efficacy or delay disease progression. Furthermore, the potential integration of cutting-edge technologies like gene editing offers an even broader toolbox for the development of even more effective and targeted treatments.

In this dynamic landscape, the interplay between innovation in biotech companies, VC, and pharma is set to continue, propelling the development and delivery of new therapies for patients. This review not only summarizes the remarkable progress of the past but also points to an even brighter future for retinal therapeutics, where science, investment, and patient care converge to redefine what is possible.

Declaration of interest

D.H., T.L, N.L, G.J.M. are employed on a full-time basis by Forbion, a venture capital firm specializing in investment within the life sciences sector. Forbion engages in the funding of various life science companies, including Oxular Limited, Complement Therapeutics GmbH, AAVantgarde Bio Srl, and Gyroscope Therapeutics Limited, which were highlighted in this review. S.C is co-founder of Complement Therapeutics GmbH. The analyses and information presented in this review are intended for informational purposes only and should not be interpreted as financial advice.

CRediT authorship contribution statement

Dmitrij Hristodorov: Conceptualization, Data curation, Visualization, Writing – original draft, Writing – review & editing. **Tim Lohoff:** Data curation, Formal analysis, Visualization, Writing – original draft, Writing – review & editing. **Nanna Luneborg:** Conceptualization, Writing – original draft. **Geert-Jan Mulder:** Writing – original draft. **Simon J. Clark:** Conceptualization, Data curation, Visualization, Writing – original draft, Writing – review & editing.

Data availability

All data was derived from databases and can be shared as Excel tables.

References

AAVantgarde Bio. Homepage - AAVantgarde bio (no date). https://www.aavantgardebio.com/. (Accessed 3 January 2024).

Abeona Therapeutics. Abeona therapeutics Inc. (ABEO) (no date). https://www.abeonatherapeutics.com/science#pipeline. (Accessed 3 January 2024).

Adams, B., 2022. Roche's Susvimo struggles for traction with eye doctors, Fierce Pharma. https://www.fiercepharma.com/marketing/roches-susvimo-struggling-traction-eye-doctors. (Accessed 2 January 2024).

Alkahest. Clinical progress - alkahest (no date). https://www.alkahest.com/pipeline/clinical-progress/. (Accessed 3 January 2024).

Alkeus Pharmaceuticals, 2023. Alkeus pharmaceuticals presents positive gildeuretinol trial results at American academy of ophthalmology, demonstrating significant slowing of retinal atrophic lesions in Stargardt disease. https://alkeuspharma.com/alkeus-pharmaceuticals-presents-positive-gildeuretinol-trial-results-at-american-academy-of-ophthalmology-demonstrating-significant-slowing-of-retinal-atrophic-lesions-in-stargardt-disease/. (Accessed 3 January 2024).

Allikmets, R., et al., 1997. A photoreceptor cell-specific ATP-binding transporter gene (ABCR) is mutated in recessive Stargardt macular dystrophy. Nat. Genet. 15 (3), 236–246. https://doi.org/10.1038/NG0397-236.

Alshaikh, R.A., Waeber, C., Ryan, K.B., 2022. Polymer based sustained drug delivery to the ocular posterior segment: barriers and future opportunities for the treatment of neovascular pathologies. Adv. Drug Deliv. Rev. 187, 114342 https://doi.org/10.1016/J.ADDR.2022.114342.

Annexon Biosciences Inc, 2023. Annexon presents ARCHER trial results at ASRS 2023 highlighting potential of ANX007 as a differentiated treatment for geographic atrophy. https://ir.annexonbio.com/news-releases/news-release-details/annexon-presents-archer-trial-results-asrs-2023-highlighting. (Accessed 8 October 2023).

Anzalone, A.V., et al., 2019. Search-and-replace genome editing without double-strand breaks or donor DNA. Nature 149–157. https://doi.org/10.1038/s41586-019-1711-4, 2019 576:7785, 576(7785.

Anzalone, A.V., Koblan, L.W., Liu, D.R., 2020. Genome editing with CRISPR–Cas nucleases, base editors, transposases and prime editors. Nat. Biotechnol. 38 (7), 824–844. https://doi.org/10.1038/s41587-020-0561-9, 2020 38:7.

Apellis, 2023. FDA approves SYFOVRE™ (pegcetacoplan injection) as the First and only Treatment for geographic atrophy (GA), a leading Cause of blindness. https://investors.apellis.com/news-releases/news-release-details/fda-approves-syfovretm-pegcetacoplan-injection-first-and-only. (Accessed 8 October 2023).

Apellis Pharmaceuticals, 2023a. Apellis provides update on review of rare safety events with SYFOVRE® (pegcetacoplan injection) for geographic atrophy - Apellis pharmaceuticals, Inc. https://investors.apellis.com/news-releases/news-release-details/apellis-provides-update-review-rare-safety-events-syfovrer. (Accessed 3 January 2024).

Apellis Pharmaceuticals, 2023c. 'NDA 217171 - syfovre', FDA [Preprint]. www.fda.gov/medwatch. (Accessed 3 January 2024).

Armento, A., Ueffing, M., Clark, S.J., 2021. The complement system in age-related macular degeneration. Cell. Mol. Life Sci. : CM 78 (10), 4487–4505. https://doi.org/10.1007/S00018-021-03796-9.

Ascidian Therapeutics. Ascidian therapeutics (no date). https://ascidian-tx.com/programs/. (Accessed 3 January 2024).

Avery, R., 2021. Two year results from the subretinal RGX-314 gene therapy phase 1/2a study for the treatment of neovascular AMD, and an update on suprachoroidal trials. https://www.regenxbio.com/getmedia/d311cd48-532b-49ac-bf41-59d3d8907c8d/RGX-314_BobAvery-AAO-2021_11Nov21_FINAL.pdf?ext=.pdf. (Accessed 2 January 2024).

Baumal, C.R., et al., 2020. Retinal vasculitis and intraocular inflammation after intravitreal injection of brolucizumab. Ophthalmology 127 (10), 1345–1359. https://doi.org/10.1016/j.ophtha.2020.04.017.

Belite Bio. Product 008 | belite bio (no date). https://belitebio.com/product-008/. (Accessed 3 January 2024).

BIO, QLS Advisors and Informa UK Ltd, 2021. Clinical development success rates and contributing factors 2011-2020. https://go.bio.org/rs/490-EHZ-999/images/ClinicalDevelopmentSuccessRates2011_2020.pdf. (Accessed 2 January 2024).

Cao, Y., Langer, R., Ferrara, N., 2023. 'Targeting angiogenesis in oncology, ophthalmology and beyond'. Nat. Rev. Drug Discov. 22 (6), 476–495. https://doi.org/10.1038/s41573-023-00671-z, 2023 22:6.

Carroll, J., 2014. Novartis hands Ophthotech a $1B deal for heavyweight wet AMD contender. https://www.fiercebiotech.com/biotech/novartis-hands-ophthotech-a-1b-deal-for-heavyweight-wet-amd-contender. (Accessed 11 October 2023).

Chirco, K.R., et al., 2016. Selective accumulation of the complement membrane attack complex in aging choriocapillaris. Exp. Eye Res. 146, 393. https://doi.org/10.1016/J.EXER.2015.09.003.

Chong, V., 2015. Ranibizumab for the treatment of wet AMD: a summary of real-world studies. Eye 30 (2), 270–286. https://doi.org/10.1038/eye.2015.217, 2016 30:2.

Cipriani, V., et al., 2020. Increased circulating levels of Factor H-Related Protein 4 are strongly associated with age-related macular degeneration. Nat. Commun. 11 (1), 778. https://doi.org/10.1038/s41467-020-14499-3.

Cipriani, V., et al., 2021. 'Beyond Factor H: the influence of genetic variation with age-related macular degeneration on circulating Factor H-like 1 and Factor H-related protein levels'. American journal of human genetics. https://doi.org/10.1016/J.AJHG.2021.05.015.

Clark, S.J., et al., 2006. His-384 allotypic variant of factor H associated with age-related macular degeneration has different heparin binding properties from the non-disease-associated form. J. Biol. Chem. 281 (34), 24713–24720. https://doi.org/10.1074/jbc.M605083200.

Clark, S.J., et al., 2010. Impaired binding of the age-related macular degeneration-associated complement factor H 402H allotype to Bruch's membrane in human retina. J. Biol. Chem. 285 (39), 30192–30202. https://doi.org/10.1074/jbc.M110.103986.

Clark, S.J., et al., 2013. Tissue-specific host recognition by complement factor H is mediated by differential activities of its glycosaminoglycan-binding regions. J. Immunol. 190 (5), 2049–2057. https://doi.org/10.4049/jimmunol.1201751.

Clark, S.J., et al., 2014. Identification of factor H–like protein 1 as the predominant complement regulator in Bruch's membrane: implications for age-related macular degeneration. J. Immunol. 193 (10), 4962–4970. https://doi.org/10.4049/jimmunol.1401613.

Clark, S.J., et al., 2017. Bruch's membrane compartmentalizes complement regulation in the eye with implications for therapeutic design in age-related macular

degeneration. Front. Immunol. 8 (DEC), 1778. https://doi.org/10.3389/fimmu.2017.01778.
Cohen, M.N., et al., 2021. APEX: a phase II randomised clinical trial evaluating the safety and preliminary efficacy of oral X-82 to treat exudative age-related macular degeneration. Br. J. Ophthalmol. 105 (5), 716–722. https://doi.org/10.1136/BJOPHTHALMOL-2020-316511.
Complement Therapeutics. Complement Therapeutics – turning powerful new Complement System insights into innovative treatments (no date). https://complementtx.com/. (Accessed 3 January 2024).
Cong, L., et al., 2013. Multiplex genome engineering using CRISPR/Cas systems. Science 339 (6121), 819–823. https://doi.org/10.1126/SCIENCE.1231143/SUPPL_FILE/PAPV2.PDF.
Cornel, S., et al., 2015. 'Anti-vascular endothelial growth factor indications in ocular disease.'. Romanian journal of ophthalmology 59 (4), 235–242.
Crago, S.M., Hutton, D., 2023. Asrs 2023: pegcetacoplan vs avacincaptad pegol in patients with geographic atrophy, Ophtamology Times. https://www.ophthalmologytimes.com/view/asrs-2023-pegcetacoplan-vs-avacincaptad-pegol-in-patients-with-geographic-atrophy. (Accessed 3 January 2024).
Csaky, K.G., et al., 2015. 'Clinical evaluation of pazopanib eye drops versus ranibizumab intravitreal injections in subjects with neovascular age-related macular degeneration'. Ophthalmology 122 (3), 579–588. https://doi.org/10.1016/J.OPHTHA.2014.09.036.
Day, A.J., et al., 1988. 'Sequence polymorphism of human complement factor H.'. Immunogenetics 27 (3), 211–214.
de Jong, S., Tang, J., Clark, S.J., 2023. 'Age-related macular degeneration: a disease of extracellular complement amplification'. Immunol. Rev. 313 (1), 279–297. https://doi.org/10.1111/IMR.13145.
Demirs, J.T., et al., 2021. 'Differential and altered spatial distribution of complement expression in age-related macular degeneration'. Invest. Ophthalmol. Vis. Sci. 62 (7), 26. https://doi.org/10.1167/IOVS.62.7.26, 26.
Disc Medicine, 2022. Disc medicine announces completion of merger with Gemini therapeutics - Disc medicine Inc. https://ir.discmedicine.com/news-releases/news-release-details/disc-medicine-announces-completion-merger-gemini-therapeutics. (Accessed 3 January 2024).
Eckmiller, M.S., 2004. 'Defective cone photoreceptor cytoskeleton, alignment, feedback, and energetics can lead to energy depletion in macular degeneration'. Prog. Retin. Eye Res. 23 (5), 495–522. https://doi.org/10.1016/j.preteyeres.2004.04.005.
Editas Medicine, 2022. Editas medicine announces clinical data demonstrating proof of concept of EDIT-101 from phase 1/2 BRILLIANCE trial | Editas medicine. https://ir.editasmedicine.com/news-releases/news-release-details/editas-medicine-announces-clinical-data-demonstrating-proof. (Accessed 12 October 2023).
Edwards, A.O., et al., 2005. 'Complement factor H polymorphism and age-related macular degeneration.'. Science (New York, N.Y.) 308 (5720), 421–424. https://doi.org/10.1126/science.1110189.
Ellis, D., 2023. Exonate announces successful completion of Phase Ib/IIa trial in diabetic macular oedema, News Medical Life Sciences. https://www.news-medical.net/news/20231128/Exonate-announces-successful-completion-of-Phase-IbIIa-trial-in-diabetic-macular-oedema.aspx. (Accessed 3 January 2024).
Feldman, T., et al., 2022. 'Lipofuscin-Mediated photic stress induces a dark toxic effect on ARPE-19 cells'. Int. J. Mol. Sci. 23 (20), 12234 https://doi.org/10.3390/IJMS232012234.
Fleckenstein, M., et al., 2018. The progression of geographic atrophy secondary to age-related macular degeneration. https://doi.org/10.1016/j.ophtha.2017.08.038.
ForSight VISION4, Inc., 2017. ForSight VISION4, Inc. Announces acquisition by Roche. Available at: https://www.prnewswire.com/news-releases/forsight-vision4-inc-announces-acquisition-by-roche-300388249.html. (Accessed 2 January 2024).
Fritsche, L.G., et al., 2016. 'A large genome-wide association study of age-related macular degeneration highlights contributions of rare and common variants'. Nat. Genet. 48 (2), 134–143. https://doi.org/10.1038/ng.3448.
Fujinami, K., et al., 2023. 'Stargardt macular dystrophy and therapeutic approaches'. The British journal of ophthalmology [Preprint]. https://doi.org/10.1136/BJO-2022-323071.
Garcia, J., et al., 2020. 'Bevacizumab (Avastin®) in cancer treatment: a review of 15 years of clinical experience and future outlook'. Cancer Treat Rev. 86 https://doi.org/10.1016/J.CTRV.2020.102017.
Gardner, Jonathan, 2021. Roche writes off $3B on lower sales forecasts for gene therapies, cancer drugs | BioPharma Dive, Biopharma Dive. Available at: https://www.biopharmadive.com/news/roche-impairment-write-down-spark-gene-therapy/641939/. (Accessed 2 January 2024).
Gimbrone, M.A., et al., 1972. 'Tumor dormancy in vivo by prevention of neovascularization'. J. Exp. Med. 136 (2), 261–276. https://doi.org/10.1084/jem.136.2.261.
Hageman, G.S., et al., 2005. 'A common haplotype in the complement regulatory gene factor H (HF1/CFH) predisposes individuals to age-related macular degeneration.'. Proc. Natl. Acad. Sci. U.S.A. 102 (20), 7227–7232. https://doi.org/10.1073/pnas.0501536102.
Haines, J.L., et al., 2005. 'Complement factor H variant increases the risk of age-related macular degeneration.'. Science (New York, N.Y.) 308 (5720), 419–421. https://doi.org/10.1126/science.1110359.
Hallam, T.M., et al., 2020. 'Rare genetic variants in complement factor i lead to low FI plasma levels resulting in increased risk of age-related macular degeneration'. Invest. Ophthalmol. Vis. Sci. 61 (6), 18. https://doi.org/10.1167/IOVS.61.6.18, 18.
Haug, S.J., et al., 2020. 'Retinal arterial occlusive vasculitis following intravitreal brolucizumab administration'. Am. J. Ophthalmol. case reports 18. https://doi.org/10.1016/J.AJOC.2020.100680.
Heath Jeffery, R.C., et al., 2021. Inherited retinal diseases are the most common cause of blindness in the working-age population in Australia. Ophthalmic Genet. 42 (4), 431–439. https://doi.org/10.1080/13816810.2021.1913610.
Heier, J.S., et al., 2012. 'Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration'. Ophthalmology 119 (12), 2537–2548. https://doi.org/10.1016/J.OPHTHA.2012.09.006.
Holekamp, N.M., et al., 2022. 'Archway randomized phase 3 trial of the port delivery system with ranibizumab for neovascular age-related macular degeneration'. Ophthalmology 129 (3), 295–307. https://doi.org/10.1016/J.OPHTHA.2021.09.016.
Holz, F.G., et al., 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 (6), 666. https://doi.org/10.1001/JAMAOPHTHALMOL.2018.1544.
Ikarovec. Programmes - Ikarovec (no date). https://ikarovec.com/programmes/. (Accessed 3 January 2024).
Iveric Bio. Iveric (no date). https://ivericbio.com/our-science/#pipeline. (Accessed 3 January 2024).
IVERIC bio, 2023. Nda 217225 - izervay. www.fda.gov/medwatch. (Accessed 3 January 2024).
JA, W., et al., 2015. 'Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema'. N. Engl. J. Med. 372 (13), 1193–1203. https://doi.org/10.1056/NEJMOA1414264.
Jaffe, G.J., et al., 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, 10.1016/j.ophtha.2020.08.027.jCyte (no date) jCyte Inc. https://www.jcyte.com/. (Accessed 3 January 2024).
jCyte. jCyte Inc (no date). https://www.jcyte.com/. (Accessed 3 January 2024).
Jinek, M., et al., 2012. 'A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity'. Science 337 (6096), 816–821. https://doi.org/10.1126/SCIENCE.1225829/SUPPL_FILE/JINEK.SM.PDF.
Johnson & Johnson, 2020. Janssen acquires rights to novel gene therapy, pioneering treatment solutions for late-stage age-related macular degeneration. Available at: https://www.jnj.com/janssen-acquires-rights-to-novel-gene-therapy-pioneering-treatment-solutions-for-late-stage-age-related-macular-degeneration. (Accessed 3 January 2024).
Joussen, A.M., et al., 2019. 'The Developing Regorafenib Eye drops for neovascular Age-related Macular degeneration (DREAM) study: an open-label phase II trial'. Br. J. Clin. Pharmacol. 85 (2), 347. https://doi.org/10.1111/BCP.13794.
Julien-Schraermeyer, S., et al., 2020. 'Penetration, distribution, and elimination of remofuscin/soraprazan in Stargardt mouse eyes following a single intravitreal injection using pharmacokinetics and transmission electron microscopic autoradiography: implication for the local treatment of Stargardt's disease and dry age-related macular degeneration'. Pharmacol. Res. Perspect. 8 (6) https://doi.org/10.1002/PRP2.683.
Khanani, A.M., et al., 2021. 'End-of-Study results for the ladder phase 2 trial of the port delivery system with ranibizumab for neovascular age-related macular degeneration'. Ophthalmol. Retina 5 (8), 775–787. https://doi.org/10.1016/J.ORET.2020.11.004.
Khanani, A.M., et al., 2023. 'Efficacy and safety of avacincaptad pegol in patients with geographic atrophy (GATHER2): 12-month results from a randomised, double-masked, phase 3 trial', *the Lancet*, 0(0). https://doi.org/10.1016/s0140-6736(23)01583-0.
Kim, L.A., D'Amore, P.A., 2012. 'A brief history of anti-VEGF for the treatment of ocular angiogenesis'. Am. J. Pathol. 181 (2), 376–379. https://doi.org/10.1016/j.ajpath.2012.06.006.
Klein, R.J., et al., 2005. 'Complement factor H polymorphism in age-related macular degeneration.'. Science (New York, N.Y.) 308 (5720), 385–389. https://doi.org/10.1126/science.1109557.
Knickelbein, J.E., Chew, E.Y., Sen, H.N., 2016. 'Intraocular inflammation following intravitreal injection of anti-VEGF medications for neovascular age-related macular degeneration'. Ophthalmic Epidemiol. 23 (2), 69. https://doi.org/10.3109/09286586.2015.1122067.
Kodiak Sciences Inc, 2023. Kodiak Reboots Tarcocimab Tedromer Development Program Following Strong Positive Results in Phase 3 Diabetic Retinopathy GLOW Study and Following Dialogue with US Regulatory Authorities on a Regulatory Pathway for BLA Submission. Kodiak Sciences Inc. Available at: https://ir.kodiak.com/news-releases/news-release-details/kodiak-reboots-tarcocimab-tedromer-development-program-following. (Accessed 2 January 2024).
Kodiak Sciences Inc, 2023. Kodiak Sciences Announces Topline Results from its Phase 3 Studies of Tarcocimab Tedromer in Neovascular Age-Related Macular Degeneration and Diabetic Macular Edema and Provides Update on Tarcocimab Development Program.
Komor, A.C., et al., 2016. 'Programmable editing of a target base in genomic DNA without double-stranded DNA cleavage'. Nature 420–424. https://doi.org/10.1038/nature17946, 2015 533:7603, 533(7603).
Krzystolik, M.G., et al., 2002. 'Prevention of experimental choroidal neovascularization with intravitreal anti-vascular endothelial growth factor antibody fragment'. Arch. Ophthalmol. 120 (3), 338–346. https://doi.org/10.1001/archopht.120.3.338.
Kubota Vision, 2018. Safety and efficacy of emixustat in Stargardt disease, ClinicalTrials.gov. Available at: https://clinicaltrials.gov/study/NCT03772665?term=NCT03772665&rank=1. (Accessed 3 January 2024).
Lorés-Motta, L., et al., 2021. 'Common haplotypes at the CFH locus and low-frequency variants in CFHR2 and CFHR5 associate with systemic FHR concentrations and age-related macular degeneration'. The Am. J. Human Genetics [Preprint]. https://doi.org/10.1016/J.AJHG.2021.06.002.

Lyzogubov, V.V., et al., 2014. 'Polyethylene glycol induced mouse model of retinal degeneration'. Exp. Eye Res. 127, 143–152. https://doi.org/10.1016/j.exer.2014.07.021.
Macular Society, 2021. Stargardt disease - macular society. Available at: https://www.macularsociety.org/macular-disease/macular-conditions/stargardt-disease/. (Accessed 3 January 2024).
Maeder, M.L., et al., 2019. 'Development of a gene-editing approach to restore vision loss in Leber congenital amaurosis type 10'. Nat. Med. 25 (2), 229–233. https://doi.org/10.1038/s41591-018-0327-9, 2019 25:2.
Maguire, A.M., et al., 2021. Clinical perspective: treating RPE65-associated retinal dystrophy. Mol. Ther. : the journal of the American Society of Gene Therapy 29 (2), 442–463. https://doi.org/10.1016/J.YMTHE.2020.11.029.
Martin, D.F., et al., 2012a. 'Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results'. Ophthalmology 119 (7), 1388–1398. https://doi.org/10.1016/J.OPHTHA.2012.03.053.
McGregor, J.E., et al., 2020. 'Optogenetic restoration of retinal ganglion cell activity in the living primate'. Nat. Commun. 11 (1), 1–9. https://doi.org/10.1038/s41467-020-15317-6, 2020 11:1.
Menny, A., et al., 2018. 'CryoEM reveals how the complement membrane attack complex ruptures lipid bilayers'. Nat. Commun. 9 (1), 1–11. https://doi.org/10.1038/s41467-018-07653-5, 2018 9:1.
Moreno, T.A., Kim, S.J., 2016. 'Ranibizumab (Lucentis) versus bevacizumab (Avastin) for the treatment of age-related macular degeneration: an economic disparity of eye health'. Semin. Ophthalmol. 31 (4), 378–384. https://doi.org/10.3109/08820538.2016.1154174.
Mullins, Robert F., et al., 2014. 'The membrane attack complex in aging human choriocapillaris'. Am. J. Pathol. 184 (11), 3142–3153. https://doi.org/10.1016/j.ajpath.2014.07.017.
Nanoscope Therapeutics. Pipeline - nanoscope therapeutics (no date). https://nanostherapeutics.com/pipeline/. (Accessed 3 January 2024).
Ng, E.W.M., et al., 2006. 'Pegaptanib, a targeted anti-VEGF aptamer for ocular vascular disease'. Nat. Rev. Drug Discov. 5 (2), 123–132. https://doi.org/10.1038/NRD1955.
Nguyen, Q.D., et al., 2020. 'Brolucizumab: evolution through preclinical and clinical studies and the implications for the management of neovascular age-related macular degeneration'. Ophthalmology 127 (7), 963–976. https://doi.org/10.1016/J.OPHTHA.2019.12.031.
Novartis, 2018. Novartis exclusively licenses first ophthalmology gene therapy in all markets outside the US, a milestone for patients with rare inherited vision loss. Available at: https://www.novartis.com/news/media-releases/novartis-exclusively-licenses-first-ophthalmology-gene-therapy-all-markets-outside-us-milestone-patients-rare-inherited-vision-loss. (Accessed 8 October 2023).
Novartis, 2023. GT005 (PPY988): development program in geographic atrophy. Available at: https://www.novartis.com/news/gt005-ppy988-development-program-geographic-atrophy. (Accessed 13 October 2023).
Ocuphire Pharma, 2023. Ocuphire Pharma Announces Successful End-of-phase 2 Meeting with FDA for Oral APX3330 in Diabetic Retinopathy. Ocuphire Pharma, Inc. *(OCUP)* Available at: https://www.ocuphire.com/news-media/press-releases/detail/420/ocuphire-pharma-announces-successful-end-of-phase-2-meeting. (Accessed 3 January 2024)
PanOptica. PanOptica - a new wave of innovation in neovascular eye disease (no date). https://www.panopticapharma.com/. (Accessed 3 January 2024).
Parente, R., et al., 2017. 'Complement factor H in host defense and immune evasion'. Cell. Mol. Life Sci. 74 (9), 1605–1624. https://doi.org/10.1007/s00018-016-2418-4.
Perrault, I., et al., 1999. 'Leber congenital amaurosis'. Mol. Genet. Metabol. 68 (2), 200–208. https://doi.org/10.1006/MGME.1999.2906.
Presta, L.G., et al., 1997. Humanization of an anti-vascular endothelial growth factor monoclonal antibody for the therapy of solid tumors and other disorders. Cancer Res. 57, 4593–4599. http://aacrjournals.org/cancerres/article-pdf/57/20/4593/2464759/cr0570204593.pdf. (Accessed 4 January 2024).
Prime Medicine, 2023. Prime medicine presents first in vivo proof-of-concept prime editing data demonstrating ability of prime editors to treat ophthalmological diseases. Available at: https://investors.primemedicine.com/news-releases/news-release-details/prime-medicine-presents-first-vivo-proof-concept-prime-editing. (Accessed 28 October 2023).
Prosser, B.E., et al., 2007. 'Structural basis for complement factor H linked age-related macular degeneration.'. J. Exp. Med. 204 (10), 2277–2283. https://doi.org/10.1084/jem.20071069.
Rafael, D., et al., 2023. 'Delivery systems in ocular retinopathies: the promising future of intravitreal hydrogels as sustained-release scaffolds'. Pharmaceutics 15 (5), 1484. https://doi.org/10.3390/PHARMACEUTICS15051484, 2023, Vol. 15, Page *1484*.
Raftery, J., et al., 2007. 'Ranibizumab (Lucentis) versus bevacizumab (Avastin): modelling cost effectiveness'. Br. J. Ophthalmol. 91 (9), 1244–1246. https://doi.org/10.1136/BJO.2007.116616.
Rathi, S., et al., 2023. Therapeutic targeting of the complement system in ocular disease. Drug Discov. Today 28 (11), 103757. https://doi.org/10.1016/J.DRUDIS.2023.103757.
Regeneron, 2016. Regeneron announces phase 2 study of aflibercept Co-formulated with rinucumab (anti-PDGFR-beta) shows No benefit over aflibercept alone in neovascular age-related macular degeneration | Regeneron pharmaceuticals Inc. Available at: https://investor.regeneron.com/news-releases/news-release-details/regeneron-announces-phase-2-study-aflibercept-co-formulated/. (Accessed 2 January 2024).
Regeneron, 2023a. Two-year PULSAR Trial Results for Aflibercept 8 Mg Demonstrate Durable Vision Gains at Extended Dosing Intervals in Wet Age-Related Macular Degeneration. Regeneron Pharmaceuticals Inc. Available at: https://investor.regeneron.com/news-releases/news-release-details/two-year-pulsar-trial-results-aflibercept-8-mg-demonstrate/. (Accessed 3 January 2024).
Regeneron, 2023b. Two-year results for aflibercept 8 mg from pivotal PHOTON trial demonstrate durable vision gains at extended dosing intervals in diabetic macular edema | Regeneron pharmaceuticals Inc. https://investor.regeneron.com/news-releases/news-release-details/two-year-results-aflibercept-8-mg-pivotal-photon-trial/. (Accessed 3 January 2024).
REGENXBIO, 2021. REGENXBIO announces additional positive interim phase I/IIa and long-term follow-up data of RGX-314 for the treatment of wet AMD. https://ir.regenxbio.com/node/10111/pdf. (Accessed 2 January 2024).
ReNeuron. hRPCs for retinal disease - ReNeuron (no date). https://www.reneuron.com/products/hrpcs-for-retinitis-pigmentosa/. (Accessed 3 January 2024).
Ripoche, J., et al., 1988. 'The complete amino acid sequence of human complement factor H.'. Biochem. J. 249 (2), 593–602.
Romero-Aroca, P., et al., 2016. 'Diabetic macular edema pathophysiology: vasogenic versus inflammatory'. J. Diabetes Res. https://doi.org/10.1155/2016/2156273, 2016.
Rosenfeld, P.J., Fung, A.E., Puliafito, C.A., 2005. 'Optical coherence tomography findings after an intravitreal injection of bevacizumab (Avastin®) for macular edema from central retinal vein occlusion'. Ophthalmic Surg. Laser. Imag. 36 (4), 336–339. https://doi.org/10.3928/1542-8877-20050701-15.
Sahel, J.A., et al., 2021. 'Partial recovery of visual function in a blind patient after optogenetic therapy'. Nat. Med. 27 (7), 1223–1229. https://doi.org/10.1038/s41591-021-01351-4, 2021 27:7.
Schmidt-Ott, U., et al., 2023. 'Reported rates of intraocular inflammation with intravitreal aflibercept administered via pre-filled syringe or from vials in clinical practice between 2012 and 2022'. Clin. Ophthalmol. 17, 385. https://doi.org/10.2147/OPTH.S393519.
Schmitz-Valckenberg, S., et al., 2008. Fundus autofluorescence imaging: review and perspectives. Retina 28 (3), 385–409. https://doi.org/10.1097/IAE.0B013E318164A907. Philadelphia, Pa.
Sharma, R., et al., 2020. 'Retinal pigment epithelium replacement therapy for age-related macular degeneration: are we there yet?'. Annu. Rev. Pharmacol. Toxicol. 60, 553–572. https://doi.org/10.1146/ANNUREV-PHARMTOX-010919-023245.
Sherwood, L.M., Parris, E.E., Folkman, J., 1971. Tumor angiogenesis: therapeutic implications. N. Engl. J. Med. 285 (21), 1182–1186. https://doi.org/10.1056/nejm197111182852108.
Skei, J.M., et al., 2010. 'Complement component C5a activates ICAM-1 expression on human choroidal endothelial cells'. Invest. Ophthalmol. Vis. Sci. 51 (10), 5336–5342. https://doi.org/10.1167/IOVS.10-5322.
Spark Therapeutics, 2019. Spark therapeutics enters into definitive merger agreement with Roche. https://sparktx.com/press_releases/spark-therapeutics-enters-into-definitive-merger-agreement-with-roche/. (Accessed 8 October 2023).
SpliceBio. SpliceBio - developing next generation gene therapies (no date). https://splice.bio/. (Accessed 3 January 2024).
Stargazer Pharmaceuticals, 2020. Study of STG-001 in subjects with Stargardt disease, ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT04489511?term=STG-001&rank=1. (Accessed 3 January 2024).
Outlook Therapeutics, 2023. Outlook Therapeutics® Submits Special Protocol Assessment (SPA) to FDA for Non-inferiority Study of ONS-5010 - Outlook Therapeutics. *Inc.* Available at: https://ir.outlooktherapeutics.com/news-releases/news-release-details/outlook-therapeuticsr-submits-special-protocol-assessment-spa. (Accessed 4 January 2024).
ViGeneron (no date. ViGeneron - the next generation gene therapy companyViGeneron. Available at: https://vigeneron.com/. (Accessed 3 January 2024).
Wan, C.R., et al., 2021. 'Suprachoroidal delivery of small molecules, nanoparticles, gene and cell therapies for ocular diseases'. Pharmaceutics 13 (2), 288. https://doi.org/10.3390/PHARMACEUTICS13020288, 2021, Vol. 13, Page *288*.
Whitmore, S Scott, et al., 2015. 'Complement activation and choriocapillaris loss in early AMD: implications for pathophysiology and therapy'. Prog. Retin. Eye Res. 45, 1–29. https://doi.org/10.1016/j.preteyeres.2014.11.005.
Yaspan, B.L., et al., 2017. 'Targeting factor D of the alternative complement pathway reduces geographic atrophy progression secondary to age-related macular degeneration'. Sci. Transl. Med. 9 (395) https://doi.org/10.1126/SCITRANSLMED.AAF1443.
Yehoshua, Z., et al., 2014. 'Systemic complement inhibition with eculizumab for geographic atrophy in age-related macular degeneration: the COMPLETE study'. Ophthalmology 121 (3), 693–701. https://doi.org/10.1016/j.ophtha.2013.09.044.
Zauhar, R., et al., 2022. 'As in real estate, location matters: cellular expression of complement varies between macular and peripheral regions of the retina and supporting tissues'. Front. Immunol. 13, 895519 https://doi.org/10.3389/fimmu.2022.895519.
Zhang, J., et al., 2015. 'Molecular pharmacodynamics of emixustat in protection against retinal degeneration'. J. Clin. Investig. 125 (7), 2781. https://doi.org/10.1172/JCI80950.