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HIGHLIGHTS

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REVIEW

Complement-targeted therapeutics: Are we there yet, or just getting started?

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Therapeutic interventions in the complement system, a key immune-inflammatory mediator and contributor to a broad range of clinical conditions, have long been considered important yet challenging or even unfeasible to achieve. Almost 20 years ago, a spark was lit demonstrating the clinical and commercial viability of complement-targeted therapies. Since then, the field has experienced an impressive expansion of targeted indications and available treatment modalities. Currently, a dozen distinct complement-specific therapeutics covering several intervention points are available in the clinic, benefiting patients suffering from eight disorders, not counting numerous clinical trials and off-label uses. Observing this rapid rise of complement-targeted therapy from obscurity to mainstream with amazement, one might ask whether the peak of this development has now been reached or whether the field will continue marching on to new heights. This review looks at the milestones of complement drug discovery and development achieved so far, surveys the currently approved drug entities and indications, and ventures a glimpse into the future advancements yet to come.

Keywords: Complement system · Drug Discovery and Development · Therapeutics

Introduction

From the perspective of an academic drug discovery and development scientist, the transformation of the field of complement-targeted therapeutics has been nothing short of amazing. When sharing one's passion for developing complement drugs less than 20 years ago, you were likely confronted with the question "Why would you want to do this?", suggesting that the approach would not be safe, feasible, or remotely successful. Now, in 2024, one may still face the same question but based on the concern that there are already plenty of drugs in the clinic, and the pharmaceutical industry has firmly taken the lead. Indeed, the number of approved complement-targeted drugs has escalated over the past two decades, from none in 2004 to one in 2014, and a dozen in 2024 (Table 1).

This development, largely facilitated by the tenacity and industriousness of many academic and clinical complementologists [1], has transformed the treatment options for patients suffering from rare complement-driven disorders, raised awareness of the pathway's involvement in health and disease, and inspired exciting new research endeavors [2–4]. With all this in mind, what does the future hold for complement therapeutics? Have we reached the pinnacle and addressed all clinical needs or is there still room for improvement and for new drugs to enter the market? And will there be a role for nonindustrial research and development along the way?

Rather than providing a comprehensive overview of all aspects related to complement-targeted drug development and surveying the pipelines of pharmaceutical companies, a task already covered by many excellent reviews [2, 4–8], this essay aims to assess the current state with a focus on approved indications and treatment options, point out major advancements and potential remaining or emerging challenges, and speculate about the developments that may shape the future direction of the field.

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Table 1. Complement-specific therapeutics with market authorization (as of June 2023, sorted by date of initial approval; without biosimilars and broadband serine protease inhibitors).

Compound	Drug	Target	Modality	Mode	Indications	Approval
Eculizumab	Soliris, Alexion	C5	mAb (humanized, IgG2/4)	PPIi	PNH, aHUS, gMG, NMOSD	2007, 2011, 2017, 2019
Ravulizumab	Ultomiris, Alexion	C5	mAb (humanized, IgG2/4)	PPIi	PNH, aHUS, gMG, NMOSD	2018[a] 2019, 2022, 2024
Pegcetacoplan	Empaveli,[b] Apellis Syfovre, Apellis	C3/C3b	Peptide (macrocycle, PEGylated)	PPIi	PNH GA (AMD)	2021[c] 2023
Avacopan	Tavneos, Amgen	C5aR1	LMW	Antagonist	AAV	2021
Sutimlimab	Enjaymo, Sanofi	C1s	mAb (humanized, IgG4)	PPIi	CAD	2022
Vilobelimab	Gohibic, InflaRx	C5a	mAb (chimeric, IgG4)	PPIi	COVID-19	[2023][d]
Avacincaptad pegol	Izervay, Astellas	C5	Aptamer (PEGylated)	PPIi	GA (AMD)	2023
Pozelimab	Veopoz, Regeneron	C5	mAb (human, IgG4)	PPIi	CHAPLE	2023
Zilucoplan	Zilbrysq, UCB	C5	Peptide (macrocycle, lipidated)	PPIi	gMG	2023
Iptacopan	Fabhalta, Novartis	FB	LMW	Inhibitor	PNH	2023
Crovalimab	PiaSky, Chugai/Roche	C5	mAb (humanized, IgG1/4)	PPIi	PNH	2024
Danicopan	Voydeya, Alexion	FD	LMW	Inhibitor	PNH	2024

Abbreviations: AAV, anti-neutrophil antibody-associated vasculitis; aHUS, atypical hemolytic uremic syndrome; AMD, age-related macular degeneration; CAD, cold agglutinin disease; CHAPLE, CD55 deficiency with complement hyperactivation, angiopathic thrombosis, and protein-losing enteropathy; GA, geographic atrophy; gMG, generalized myasthenia gravis; LMW, low molecular weight compound; mAb, monoclonal antibody; NMOSD, neuromyelitis optica system disorder; PEG, polyethylene glycol; PNH, paroxysmal nocturnal hemoglobinuria; PPIi, protein–protein interaction inhibitor.

[a] Initial approval for adults with PNH; approval for children and adolescents with PNH in 2021. An advanced formulation with reduced infusion time (Ultomiris-cwvz) was approved in 2020.

[b] Branded as Aspaveli (Apellis/Sobi) in some markets.

[c] Empaveli injector was approved in 2023.

[d] Gohibic is not yet approved but only received emergency use authorization.

CSI: amazing — a brief history of complement system inhibition

Despite the actual introduction of clinical complement inhibitors being a relatively recent advancement, the idea of therapeutically modulating the complement system has been a long time coming [9]. Shortly after the initial description of the pathway as a "complementary" effector arm to antibodies in the killing of bacteria [10, 11], reports emerged that complement activation is also observed in noninfectious malignancies [12]. The complement system's Janus-faced role in host defense and attack has been continuously solidified over the decades, and it is now recognized as a contributing factor in many autoimmune, inflammatory, and hemolytic disorders, as well as in age-, biomaterial-, and transplantation-related conditions [2, 3, 9]. Yet, notwithstanding initial nonselective modalities such as C1 esterase inhibitor preparations, the first complement-specific drug only entered the clinic in 2007 — a mere century after the identification of complement as a potential target system [13, 14]. The reasons for this delay and the emerging role of complement as a "therapeutic platform" are founded in the elaborate mechanisms that define complement's involvement in host defense and attack. The following section will focus on essential concepts of complement activation and regulation, and refer to other work for in-depth coverage [2, 15, 16].

Similar to the coagulation system, the complement system is organized as a cascade that enables the rapid amplification of small triggering events into a profound effector response with the primary goal of eliminating microbial intruders and alerting companion defense pathways (Fig. 1A) [2, 9]. Under ideal conditions, a panel of circulating pattern recognition receptors detect foreign or damaged cells by binding to antibody clusters (i.e. classical pathway [CP]) or carbohydrate signatures (i.e. lectin pathway [LP]), and activate associated serine proteases. Such sensing events lead to the cleavage of complement components C4 and C2 and the deposition of C3 convertase complexes on the triggering surface. Additional convertases may form through the alternative pathway (AP), when the abundant plasma protein C3 is hydrolyzed at low rates in solution (i.e. tick-over) or adheres to surfaces. Independent of their origin, C3 convertases cleave C3 into the anaphylatoxin C3a and the surface-tethered opsonin C3b. If left unchecked, this initial opsonization rapidly propagates, as deposited C3b can form additional C3 convertases and drive an amplification cycle that fuels effector generation. With mounting opsonin densities, convertases start to increasingly cleave C5, which initiates the assembly of porous membrane-

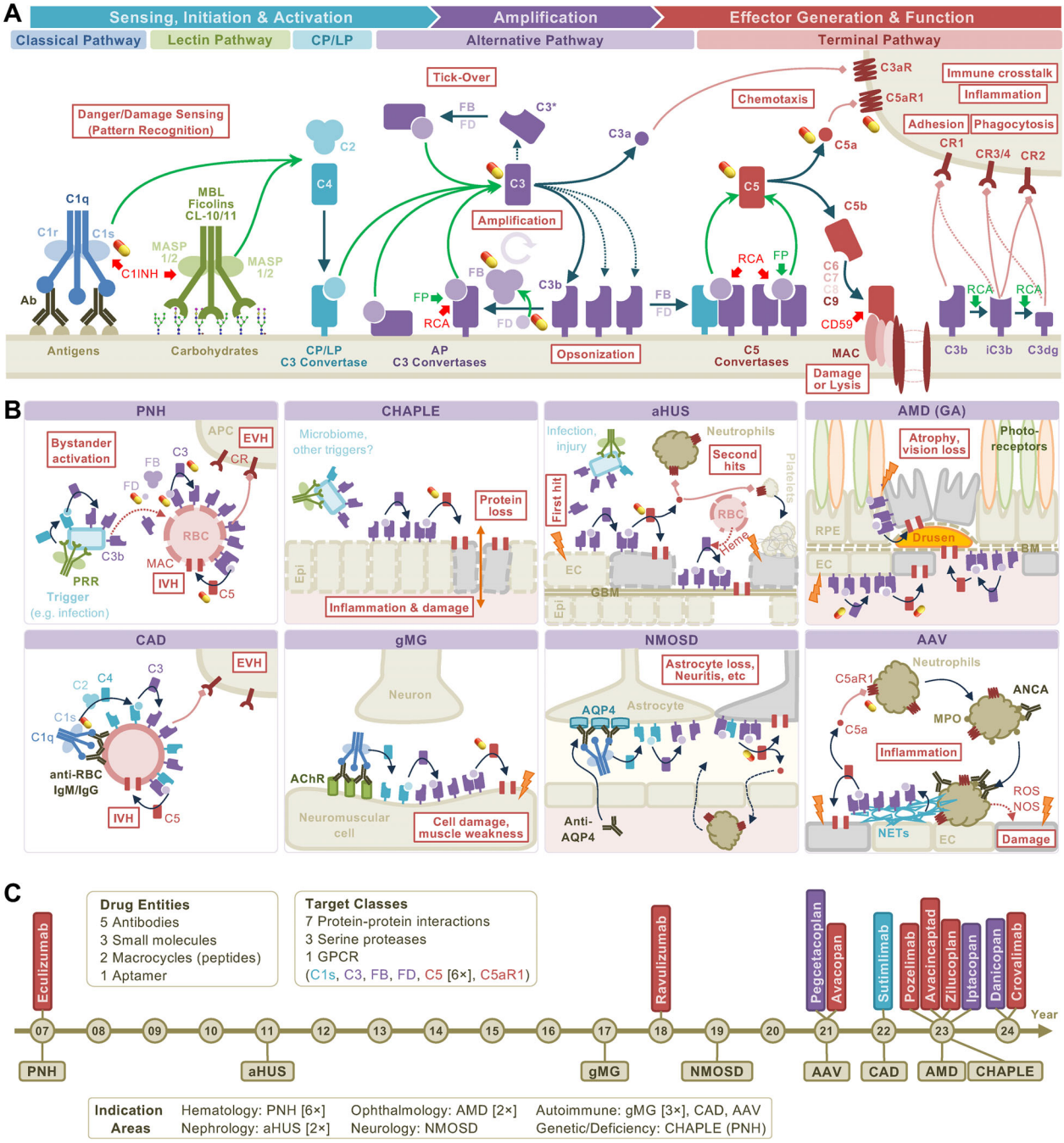


Figure 1. Complement activation and therapeutic intervention. (A) Simplified depiction of cell surface-targeted complement activation. Targets of complement therapeutics that have been approved or authorized for use are marked by a capsule symbol. (B) General mechanisms of complement-related indications with approved treatment options. Solid and dashed cell membranes depict sufficiently and insufficiently protected cell surfaces, respectively (due to polymorphic or missing regulators). Grey cells reflect dysfunctional and/or apoptotic cells, and orange flash symbols indicate tissue damage. (B) Timeline of complement-targeted therapeutics in the clinic, showing drug approvals (top) and indication extension (bottom). Only officially approved complement-specific drugs are shown, omitting C1 esterase inhibitor (C1-INH) preparations, eculizumab biosimilars, and emergency use authorizations (Table 1; as of May 2024). Timeline number correspond to years between 2007 and 2024. AAV, ANCA-associated vasculitis; Ab, antibody; AChR, acetylcholine receptor; aHUS, atypical hemolytic uremic syndrome; AMD, age-related macular degeneration; ANCA, antineutrophil cytoplasmic antibody; AP, alternative pathway; AQP4, aquaporin-4; BM, Bruch's membrane; C1-INH, C1 esterase inhibitor; C3aR, C3a receptor; C5aR1, C5a receptor 1; CAD, cold agglutinin disease; CHAPLE, CD55 deficiency with hyperactivation of complement, angiopathic thrombosis, and protein-losing enteropathy; CL-10/11, collectin-10/11; CP, classical pathway; CR1-4; complement receptor 1–4; EC, endothelial cell; Epi, epithelial cell; EVH, extravascular hemolysis; FB, factor B; FD, factor D; GA, geographic atrophy; GBM, glomerular basement membrane; gMG, generalized myasthenia gravis; GPCR, G protein-coupled receptor; IVH, intravascular hemolysis; LP, lectin pathway; MAC, membrane-attack complex; MASP, MBL-associated serine protease; MBL, mannose-binding lectin; MPO, myeloperoxidase; NET, neutrophil extracellular trap; NMOSD, neuromyelitis optica system disorders; PNH, paroxysmal nocturnal hemoglobinuria; RCA, regulators of complement activation; ROS, reactive oxygen species.

attack complexes (MAC) with cell-damaging or even lytic impact. Complement activation also releases anaphylatoxins (i.e. C3a and C5a) that attract, activate, and/or modulate a variety of effector cells, including leukocytes, endothelial cells (ECs), and platelets. Through binding to complement receptors (CR1-4) on immune cells, opsonins can further shape the cellular response and induce phagocytosis (Fig. 1A).

While this elaborate interplay between sensing, propagation, and effector mechanisms enables a broad and rapid antimicrobial defense, complement's versatility comes at the expense of specificity, with an associated risk of collateral damage [3, 4]. To account for such hazards, our bodies are equipped with soluble and membrane-bound regulators that impair convertase and MAC formation or limit the activity of initiating proteases. While sufficient under normal circumstances, these regulatory capacities are not unlimited, and any tipping of the activation–regulation balance can quickly escalate to clinical complications (Fig. 1B) [3, 9]. Excessive activation, for example, due to infections, trauma, or blood contact with foreign materials, can trigger fulminant complement responses and host defense cross-talk that may result in tissue damage and thrombo-inflammatory complications. Similarly, autoantibodies can direct CP activation to host cells, inducing damage or lysis. Finally, deficiencies, polymorphisms, and other genetic variations in the various complement system components have a direct impact on an individual's activating and regulatory capacity, with implications for host defense, the clearance of cellular debris and immune complexes, and susceptibility to chronic complementopathies. Given the complement system's versatility in sensing any type of non- or altered-self surfaces and the many processes that could derail, it is not surprising that complement dysregulation has been identified as a disease-contributing factor in a broad spectrum of clinical conditions [2–4, 9].

Although this platform position of complement as a target system may provide ample therapeutic opportunities, selecting the ideal indication has proven challenging [8]. To ensure commercial sustainability, initial efforts aimed at developing complement therapeutics for prevalent conditions such as rheumatoid arthritis or complications caused by cardiopulmonary bypass surgery and transplantation [13]. Given the complexity of these conditions and the varying role that complement may play in their pathology, it is understandable that success has been limited. Additionally, lingering concerns that any blockade of a host defense system could result in severe infections and other adverse events kept complement drug development off the radar of pharmaceutical companies. The eventual breakthrough of the approach can be attributed to many factors. Despite restrained interest from big pharma, academic and clinical researchers continued to elucidate mechanisms of complement activation in health and disease, develop various inhibitors, and elaborate on potential treatment strategies [1]. At the same time, the emergence of biotech companies as important players in drug development, the rise of monoclonal antibodies (mAb) as accessible and safe treatment modalities, and the implementation of orphan drug acts in various markets provided incentives to develop therapeutics for rare and/or neglected conditions [17, 18].

On the path toward the first approved complement-specific drug in 2007 (Fig. 1C) [14], Alexion virtuously tapped into several of these developments. Rather than targeting prevalent disorders, the company finally focused on paroxysmal nocturnal hemoglobinuria, an ultrarare disease with limited treatment options but well-understood and exclusively complement-driven pathophysiology [14]. Mechanistic insight previously identified complement component C5 as a key contributor to the pathophysiology of PNH [19], and murine anti-C5 mAbs were reported by academic groups [20, 21]. In clinical trials, the anti-C5 mAb eculizumab (Soliris) not only proved highly effective, providing PNH patients with the long-sought treatment option, but also demonstrated a remarkably beneficial safety profile [14]. Neisserial infections presented a substantial risk that could be largely mitigated through vaccination and reserve antibiotics [22]. While far from being a perfect drug, especially considering the exorbitant cost at the time of introduction [23], the rather high, frequent, and inconvenient dosing, and the limited response in some patients, the approval of eculizumab marked a watershed moment for PNH patients and the entire field of complement-targeted therapies.

The clinical and commercial success of eculizumab, alongside a revised risk assessment of the approach, encouraged biotech and pharmaceutical companies to continue or initiate complement-targeted development programs. The almost 15-year gap between eculizumab's approval and the next first-in-class therapeutics (Fig. 1C) corresponds to typical bench-to-bedside timelines in drug development. Yet, the surge of interest in the strategy was equally rooted in prospects of navigating toward larger markets, sparked by reports that identified complement dysregulation as the main risk factor in age-related macular degeneration (AMD) [24–26], among the leading causes of blindness in elderly people. The initial enthusiasm was rapidly tamed, however, with the realization that complement processes in AMD are more complex and diverse than in PNH, leading to several failed trials, including the late-stage discontinuation of Genentech's anti-factor D (FD) program after disappointing phase 3 interim data in 2017 [27]. Fortunately, these setbacks did not halt development efforts but rather channeled the gold-rush euphoria toward more leveled yet realistic goals. Among the consequences was an even stronger focus on (ultra-)rare disease indications, which may be considered a necessary and successful strategy, at least in the short term, but may arguably have had a distracting impact on building a sustainable long-term foundation, as discussed later.

While hopes largely rested on a breakthrough in AMD, the gap years after eculizumab's approval have by no means been an idle phase. The clinical availability of a C5-targeted drug enabled expansion into other diseases with terminal pathway-driven pathologies (Fig. 1B and C), initially atypical hemolytic uremic syndrome (aHUS; 2011) [28], but later also generalized myasthenia gravis (gMG; 2017) [29] and neuromyelitis optica spectrum disorders (NMOSD; 2019) [30]. The extended approval of eculizumab in diverse indications, along with case reports of off-label use in other disorders [31], reinforced the perception of therapeutic complement inhibition

as a platform approach and contributed to continued commercial interest.

Alongside the progress in clinical applications, the approval of ravulizumab (Ultomiris) in 2018 introduced another drug to the arsenal. Even if not truly new, this eculizumab derivative featured an improved pharmacokinetic (PK) profile that addressed the inconvenient administration by prolonging infusion intervals from 2 to 8 weeks [32]. The pharmacodynamic (PD) properties remained the same, with the modality (mAb), target (C5), and even the binding site of ravulizumab corresponding to that of eculizumab. The target barrier was finally breached in 2021 with the approval of a peptidic C3 inhibitor of the compstatin family for PNH (pegcetacoplan, Empaveli) [33–35] and a C5a receptor 1 (C5aR1) antagonist for antineutrophil cytoplasmic antibody-associated vasculitis (AAV; avacopan, Tavneos) [22, 36], which interfere with central activation and amplification steps and terminal signaling events, respectively (Table 1 and Fig. 1). The approval of sutimlimab (Enjaymo) in 2022 extended the target and indication spectrum at the same time, as the mAb blocks the CP protease C1s for the treatment of cold agglutinin disease (CAD) [37, 38].

Yet, the true "annus incredibilis" came in 2023, when four new drugs and two novel indications entered the market (Fig. 1B and C). Whereas pozelimab (Veopoz) is another C5-targeted mAb, the major novelty was the indication it was approved for: CD55 deficiency with hyperactivation of complement, angiopathic thrombosis, and protein-losing enteropathy (CHAPLE) [39–41]. Another foray into new disease areas was achieved by an already approved drug (pegcetacoplan), yet in a distinct formulation suitable for the intravitreal treatment of geographic atrophy during AMD (Syfovre) [30]. With the aptamer avacincaptad pegol (Izervay), a C5-targeted drug joined the treatment options for AMD a few months later [42]. The third C5 inhibitor approved in 2023 was zilucoplan (Zilbrysq), a peptidic drug positioned for the treatment of gMG [43, 44]. Finally, PNH patients benefited from the introduction of a factor B (FB) inhibitor (iptacopan, Fabhalta) that enables oral monotherapies [45, 46].

While it remains to be seen whether the approval peak can be matched or even surpassed in 2024, the year has already welcomed two new drugs for PNH treatment. The FD inhibitor danicopan (Voydeya) was approved as an add-on therapy for PNH patients who show insufficient response to anti-C5 treatments [47, 48], whereas the anti-C5 mAb crovalimab (PiaSky) has recently been approved by the FDA following earlier authorizations in China and Japan [49, 50].

Complement as platform target system: a blessing — and a curse

The involvement of complement activation in a broad spectrum of clinical conditions makes therapeutic complement inhibition an attractive prospect [8]. However, the complexity of underlying disease mechanisms, the variability of complement contributions to pathology, and the multitude of potential intervention points have often left drug developers uncertain about the best approach. Companies have had to decide whether to target well-validated indications with largely addressed needs (e.g. PNH, aHUS) by offering improved modalities or carve out their own market niche. Target selection imposes another major challenge in most cases, given that several initiation, effector, and crosstalk pathways are often involved in disease mechanisms. Since their contributions vary between diseases and even between patients, choosing the best target is rarely obvious. Ideally, only the pathogenic effectors are impaired while other parts of the complement system are left intact to assist in immune surveillance. The decision-making process may actually start at the intervention level rather than specific targets, that is, whether to block proximal or terminal complement functions [4, 7, 9]. Inhibiting the terminal pathway at the level of C5 activation, preventing the generation of both C5a and MAC, or C5aR1 signaling is often effective in curbing cell damage and inflammation and does not directly interfere with danger sensing and opsonization. However, it still blocks some antimicrobial defense and immune crosstalk functions, and untamed opsonization on host cells may contribute to disease progression. Conversely, proximal intervention typically impairs detrimental complement activities more broadly and at an early stage, which may prevent exacerbation, but also has a stronger impact on the complement's protective functions. Even within proximal strategies, the decision between pathway-specific (i.e. CP, LP, or AP inhibitors) and central modulators (e.g. C3 or convertase inhibitors) may profoundly change the therapeutic profile. Target selection therefore benefits from a thorough understanding of disease processes but also depends on a careful risk-benefit assessment about how much complement impairment is required and tolerable for each indication. This section summarizes the common and distinct disease mechanisms behind currently targeted indications (Fig. 1B) and explores decision factors regarding strategies and intervention points.

Most currently targeted indications have well-defined complement-driven mechanisms, and the selection of PNH as the quintessential complementopathy was instrumental in the breakthrough of complement therapeutics [14]. PNH is a rare hemolytic disease characterized by clonal populations of RBCs lacking complement regulators CD55 and CD59 on their surface. The impaired control of convertase and MAC formation, respectively, renders affected RBCs vulnerable to complement attack that culminates in intravascular hemolysis (IVH). Although the triggers of hemolysis may be diverse, including bystander opsonization during infection, the processes driving IVH are well described. In the absence of sufficient regulation, C3b opsonization is quickly amplified via the AP, thereby generating C5 convertases and, consequently, lytic MAC pores [51]. As the gatekeeper of MAC formation, C5 emerged as an obvious target, and the anti-C5 mAb eculizumab effectively controlled IVH. However, a fraction of PNH patients did not experience full disease alleviation and remained transfusion-dependent [52]. Extravascular hemolysis was described as one of the mechanistic explanations for this limitation: since anti-C5 therapy halts MAC formation but not C3b deposition, opsonized RBCs are recognized

and eliminated by phagocytes [51, 53]. Proximal complement inhibition at the level of AP-mediated C3 activation was therefore hypothesized to provide more comprehensive disease management [54], and both C3 and FB inhibitors (pegcetacoplan and iptacopan, respectively) showed superiority over eculizumab in clinical trials [35, 46]. However, as often encountered in complement biology [53], this advancement came with an unexpected twist: whereas clone sizes of PNH RBC are typically well below 50%, these clones may expand to more than 95% during proximal therapies [55, 56]. While not inherently adverse, the accumulation of complement-vulnerable RBCs may increase the risk of severe hemolytic crises if complement inhibition is not maintained properly. In clinical practice, the breakthrough risk under proximal therapy appears to be manageable [57, 58] but longer experience is needed for a conclusive assessment and the underlying mechanisms of this phenomenon require further elucidation. The case of PNH underscores the importance of real clinical data, careful selection of intervention points and therapeutic modalities, and ongoing research even in well-defined complement-driven diseases. While crucial for PNH, which represents the exception rather than the norm among complementopathies, such considerations are even more vital for clinical conditions with more complex and variable pathologies [3, 4, 9].

From a mechanistic standpoint, the oldest and newest entries in the complement indication realm may share close ties. In CHAPLE, CD55 deficiency due to homozygous loss-of-function mutations renders cells more susceptible to complement-induced damage [40]. Unlike PNH, where CD59 protection is additionally impaired but only clonal populations of blood cells are affected, all cells of the body are potentially vulnerable to insufficiently controlled complement activation in CHAPLE. The impact on intestinal epithelial cells and lymphatics is particularly damaging and leads to protein-losing enteropathy and various symptoms, including abdominal pain [40]. MAC deposition detected in duodenal biopsy suggested a C5-targeted approach, with treatment using pozelimab successfully resolving clinical manifestations [39].

Another major indication involving ill-protected host cells is aHUS, a rare but strongly complement-related form of thrombotic microangiopathy [59–61]. Compared with PNH and CHAPLE, the causes of complement dysregulation in aHUS are more heterogeneous, including decreased-function polymorphisms in or autoantibodies against complement regulators, and gain-of-function mutations in C3 or FB [60, 62]. The disease primarily manifests in the kidneys, where glomerular ECs already feature a low regulatory capacity and are heavily exposed to complement components. Bystander activation or injury, such as surgery, may provide a "first hit," resulting in insufficiently controlled complement amplification, cell damage, and inflammation. Exposure to the glomerular basement membrane, devoid of regulators, may exacerbate the vicious cycle. Activation of neutrophils and platelets, for example, by anaphylatoxins, leads to the formation of neutrophil extracellular traps (NETs) and thrombi, respectively, and the mechanical disruption of RBC to a release of heme, all of which may serve as a "second hit" that adds insult to injury and drives further complement activation and tissue damage [59, 60, 62, 63]. Despite the complex and heterogeneous pathophysiology, blocking C5 has proven broadly effective in treating aHUS, likely benefiting from simultaneous impairment of MAC formation and C5a release.

Pathophysiological complexity increases further when examining geographic atrophy in AMD [64–66] and imposes challenges for therapeutic development, as evident by several unsuccessful clinical trials [67]. It is now appreciated that not all forms of AMD are complement-driven, and even in complement-related cases, various and often slowly progressing mechanisms define the outcome [64–66]. Complement deposits are typically observed on ECs of the choriocapillaris and in lipoprotein deposits (that is drusen) within the Bruch's membrane (BM), yet it remains debated whether those structures should be considered sites of initial complement dysregulation and/or later exacerbation. Similar to the case of the glomerular basement membrane in aHUS, the lack of membrane complement regulators renders the BM susceptible to complement attack; the reliance on soluble regulators like factor H (FH) and its split product FH-like protein 1 supports the risk association with FH polymorphisms. Complement activation may damage the BM and further propagate the attack to retinal tissue, contributing to atrophy and vision loss. Retinal pigment epithelium cells are the focal point of complement dysregulation, and their damage results in a gradual degeneration of photoreceptor cells [64, 66, 68]. Although activation of the CP or LP is potentially involved, amplification via the AP and resulting MAC and/or anaphylatoxin effects are considered the primary culprits. Intravitreal drugs targeting C3 (pegcetacoplan) or C5 (avacincaptad pegol) are meanwhile available, expected to benefit AMD patients, and provide clinically supported insight into this complex disorder [69].

Despite its major manifestation of complement-mediated intravascular hemolysis, CAD shares only a distant relationship in pathophysiology and treatment with PNH [70]. In this form of autoimmune hemolytic anemia, binding of IgM autoantibodies to the RBC surface at lower temperatures initiates CP activation that may exceed regulatory capacities, leading to C3b opsonization with extravascular hemolysis and MAC-mediated IVH [37, 70]. Understanding the triggering mechanisms allows for a more causative therapy at the initiation rather than the effector stage by blocking C1s using sutimlimab [37]. CAD is not the only disorder that is caused by an overwhelming complement attack of otherwise sufficiently protected cells upon autoimmune reactions. In gMG, autoantibodies against nicotinic acetylcholine receptors expressed on the postsynaptic membrane of neuromuscular junctions trigger CP-mediated complement activation, which leads to cell damage and contributes to the progressing muscle weakness in gMG [71, 72]. Although different intervention points appear feasible, only C5 is currently targeted in this disease, either by administering antibodies (eculizumab, ravulizumab) or inhibiting peptides (zilucoplan) [29, 43, 73]. The same target selection is employed for NMOSD, in which autoantibodies against aquaporin-4 bind to the water channel protein that is strongly expressed on the end feet of astrocytes [74]. While CP induction

primarily leads to MAC-mediated astrocyte loss, complement activation and consequential attraction of immune cells are also considered contributing factors to demyelination and axon damage that cause a range of symptoms, including ocular pain and vision impairment [74, 75].

The involvement of autoantibodies is also central to the pathophysiology of AAV, but follows a different mechanism [5, 36]; patients develop antineutrophil cytoplasmic antibodies that are directed against myeloperoxidase or other antigens. Stimulation of neutrophils by C5a or other triggers increases the expression of these antigens and, therefore, autoantibody binding. Affected neutrophils adhere to ECs and become further activated, causing the release of cell-damaging mediators and NET formation. NETosis can induce additional complement activation with the release of C5a that increases neutrophil stimulation and drives inflammation. Owing to the central role of C5a as an initiator and amplifier of deleterious effects in AAV, C5aR1 has emerged as a suitable intervention point and C5aR1 antagonists (avacopan) are now used as a therapeutic arm in this disease [22].

Although target selection is, or at least may appear, obvious in some of the indications, others could benefit from a reevaluation of the ideal intervention points. In many autoimmune disorders, CP-mediated initiation, AP-mediated amplification, and TP-mediated effector generation all appear as suitable options. Even in diseases where anti-C5 therapy shows strong efficacy, it is not always clear whether both the damaging effect of MAC and the inflammatory impact of C5a contribute to the disease and whether a more focused intervention (e.g. C5aR1 antagonists) would be sufficient. Alongside the target itself, the modality by which it is inhibited may also prove critical as it can determine how much of the drug will reach the site of attack and how long inhibition will last.

Inhibitors in all shapes and sizes

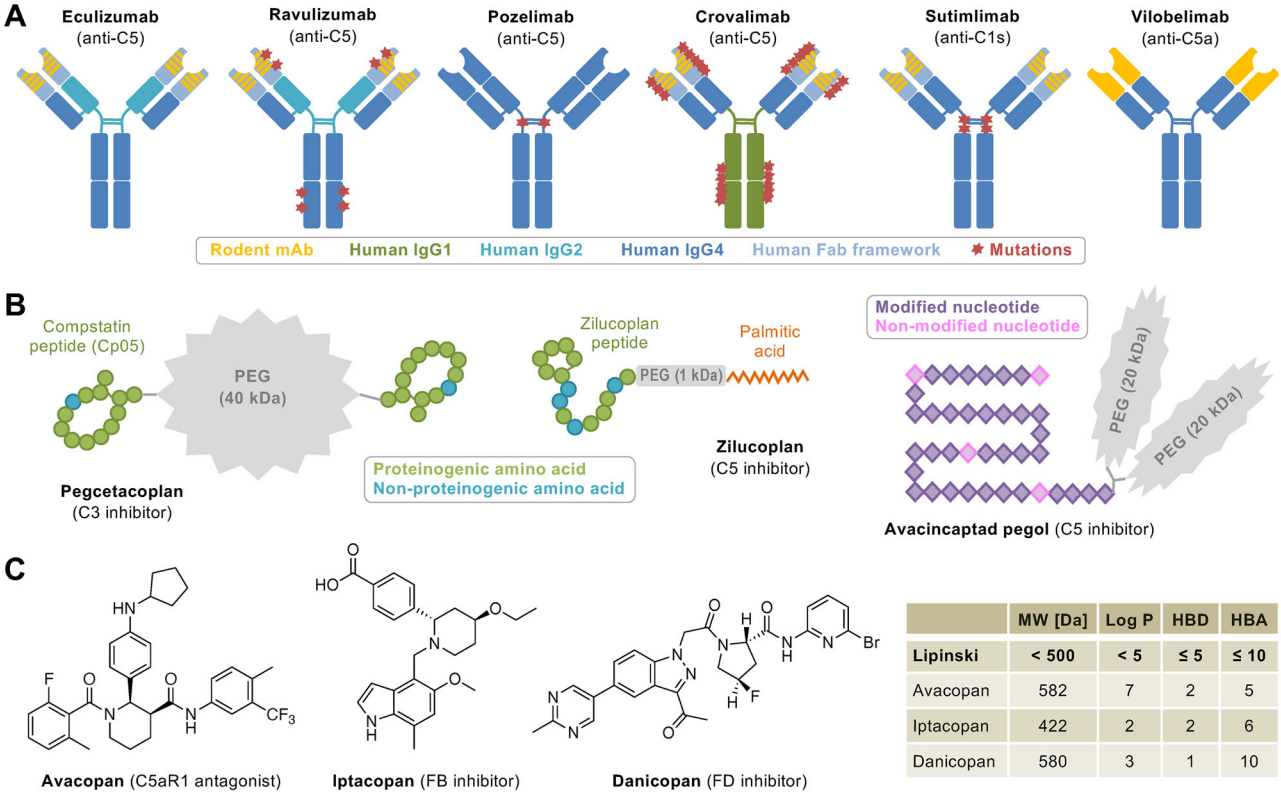
When considering the specific demands that individual complementopathies entail, it is important that recent approvals not only extend intervention points and indication areas but also bring diversification regarding molecular entities. Although antibodies still dominate the complement therapeutics arsenal, with 6 of the 12 approved drugs belonging to this class, the clinically available drugs now include two macrocyclic peptides, one aptamer, and three low-molecular-weight (LMW) drugs (Table 1, Fig. 1C and 2). This diversity is of critical importance in view of complement's platform position, as distinct modalities have an impact on PK/PD profiles and enable tailored administration options.

Even within the mAb class, considerable variability exists, with numerous modifications reflecting overarching trends in antibody drug development (Fig. 2A) [76, 77]. While many clinical antibodies originate from rodent mAbs, efforts to minimize immunogenicity and enhance PK properties have led to the development of chimeric, humanized, or fully human mAbs. Among complement therapeutics, only the anti-C5a mAb vilobelimab, which was granted emergency use authorization for COVID-19 by the FDA [78, 79], falls into the category of chimeric antibodies. All others are humanized or, in the case of pozelimab, fully human. By selecting IgG isotypes and introducing point mutations, the PK/PD profile can be further modulated. Human IgG4 is typically chosen for constant parts to avoid complement activation, but this leaves unwanted interactions with Fc-gamma receptors intact. In eculizumab, Fc-gamma receptor binding was abrogated by basing the hinge and Fab portions on human IgG2 [14], and in sutimlimab by introducing two mutations to the IgG4 hinge [80].

While antibodies generally exhibit prolonged plasma residence, their exact half-life is strongly influenced by recycling processes. Circulating antibodies are typically taken up by ECs and may undergo lysosomal degradation but can be exported back if they bind to neonatal Fc receptors (FcRn) in the endosome. Ideally, therapeutic antibodies should strongly bind their target in circulation, release it in the acidic endosome, and bind to FcRn [76, 81]. Thus, the target is degraded, and the free antibody can be recirculated to inhibit another target molecule. To obtain the long-acting derivative ravulizumab, four amino acids were changed in eculizumab: two in the variable region to enhance pH-dependent drug:target dissociation and another two in the Fc part to increase FcRn binding (Fig. 2A) [32]. More recently approved anti-C5 antibodies followed highly distinct strategies to achieve suitable properties. Pozelimab, a fully human IgG4, features only a single mutation in the hinge region to increase stability; rather than engineering PK properties during development, Regeneron employed humanized C5 mice to select an ideal candidate based on in vivo performance [82]. Conversely, crovalimab was developed using extensive mutagenesis: starting from a humanized rabbit mAb selected based on pH-dependent target release, Chugai opted for an IgG1 background and introduced numerous mutations to eliminate effector functions, reduce immunogenicity, and enhance target and FcRn binding [49, 83].

Outside the realm of antibodies, however, PK properties remain an even greater challenge. Although peptides and oligonucleotides may be classified as biologics, they are considerably smaller than mAbs and do not benefit from the intricate recycling mechanisms. To counteract rapid renal elimination, additional measures have thus been necessary [84]. In the case of pegcetacoplan, two entities of compstatin derivative Cp05, a small cyclic peptide (∼1.5 kDa) that binds C3 and C3b to impair convertase-mediated complement activation and amplification, have been conjugated to a central 40-kDa polyethylene glycol (PEG) moiety [34]. This bivalent arrangement improves pharmacokinetic properties but also appears to influence the selectivity between soluble and surface-bound targets [85]. PEGylation has similarly been pivotal in the pharmacokinetic optimization of avacincaptad pegol, an oligonucleotide aptamer that binds to C5 to prevent its activation. In contrast to pegcetacoplan, a branched PEG moiety (2×20 kDa) was selected, while the aptamer unit is presented monovalently; additionally, most of the nucleotides in avacincaptad pegol are backbone-modified to enhance stability [86].

Although PEG is generally considered a biocompatible PK modifier, it is not without risks [87], particularly considering that the administered doses for complement inhibition are often



	MW [Da]	Log P	HBD	HBA
Lipinski	**< 500**	**< 5**	**≤ 5**	**≤ 10**
Avacopan	582	7	2	5
Iptacopan	422	2	2	6
Danicopan	580	3	1	10

Figure 2. Structures of complement therapeutics that are currently approved (as of June 2024) or have been granted emergency use authorization. (A) Monoclonal antibodies as complement inhibitors. Individual domains of the depicted IgG structures are colored according to the species/isotype origin. Point mutations are marked by a star, independent of their functional implications. In the case of crovalimab, the stars may not reflect the true number and position of all modifications. (B) Peptide and aptamer drugs used as complement therapeutics. (C) Structures and properties of low-molecular-weight (LMW) complement inhibitors. For the assessment of Lipinski rule-of-5 properties [91], numbers in the table have been rounded; OH and NH groups were counted as HBD and the sum of N and O atoms as HBA; MW and log *p*-values have been derived from PubChem (www.pubchem.org). FB, factor B; FD, factor D; HBA, hydrogen bond acceptor; HBD, hydrogen bond donor; IgG, immunoglobulin G; mAb, monoclonal antibody; MW, molecular weight; PEG, polyethylene glycol.

higher than for other therapeutic areas, due to the relatively high plasma levels of many complement components. This becomes evident when examining the dosing regimen of pegcetacoplan in paroxysmal nocturnal hemoglobinuria (PNH), which requires subcutaneous administration of 1080 mg of the drug twice weekly via infusion pumps or specialized injectors to saturate circulating C3 (~1 mg/ml in plasma) [33]. Among the strategies to address this challenge is the use of compstatin derivatives with significantly improved target residence to increase inhibitory capacity while concurrently reducing unbound peptide fractions that face renal elimination [34]. A next-generation compstatin drug candidate (AMY-101, Amyndas) with enhanced target residence, which does not rely on PEGylation, is currently undergoing clinical trials for COVID-19, gingivitis, and other indications [88, 89]. A different approach to improving plasma half-life was employed during the development of zilucoplan, a cyclic peptide of ~1.5 kDa that binds to C5 at a site that interferes with both C5 activation and MAC formation. While zilucoplan does contain PEG, it primarily acts as a short spacer to connect to a glutamoyl-palmitic acid moiety that binds to human serum albumin, thereby enhancing the drug's plasma residence (Fig. 2B) [44, 86]. Depending on body weight, Zilbrysq is administered subcutaneously once daily at doses ranging between 16.6 and 32.4 mg [90]. It is important to note that dosing requirements and administration challenges vary depending on the indication; compared to the systemic use of pegcetacoplan in PNH (Empaveli; as mentioned above), the intravitreal injection for AMD treatment (Syfovre) requires only a dose of 15 mg per eye at variable frequencies, typically every 25–60 days [30]. Avacincaptad pegol is solely used for AMD therapy and necessitates an intravitreal injection of 2 mg per eye every month [42].

In contrast to biologics, which almost invariably require parenteral administration, many LMW drugs can be taken orally, enhancing convenience and therapy adherence. The currently approved LMW complement therapeutics all fall within or near the "Lipinski rules of 5" [91], a predictor of oral bioavailability (Fig. 2C). Indeed, all drugs can be administered as oral dosage forms, though not at the preferred "once-daily" dosing regimen. Treatment schemes range from one capsule twice a day (iptacopan) to three capsules twice daily (avacopan for severe active AAV) and 1–2 tablets three times a day (danicopan) [22, 46, 47]. While oral formulations render frequent dosing manageable, questions remain about therapeutic adherence by patients and the consequences of missed doses. For the latter question, the

answer may be context-specific and evolve as we gain experience using these relatively new drugs in various diseases. PNH should again be considered a special case as it relies on permanent and full complement effector function inhibition compared with other complementopathies, where activation is more transient or episodic. It is worth noting that, despite the accumulation of PNH clones and the associated risk of severe hemolytic breakthrough crises, iptacopan monotherapy has thus far proven to be an effective and safe option [46]. In the case of danicopan, positioning the drug as add-on therapy to baseline treatment with anti-C5 drugs should mitigate the risk of severe events.

In terms of their modes of action, avacopan is the only terminal pathway modulator that blocks C5a-mediated cell stimulation via C5aR1 [92]. While the FB inhibitor iptacopan and the FD inhibitor danicopan both affect AP C3 convertases and could therefore be regarded as somewhat redundant, their functional activities differ significantly [93]. During AP activation, FB interacts with surface-deposited C3b and undergoes a conformational change that enables the binding of FD, which removes the Ba fragment and produces the active convertase, C3bBb. Circulating C3 now binds to C3bBb, whereupon C3a is released by Bb-mediated cleavage and C3b is covalently deposited on the surface [94]. FD inhibitors such as danicopan impair the conversion of C3b-bound FB and prevent the formation of AP C3 convertases [48]. Although termed FB inhibitor, iptacopan's functional target is actually the Bb fragment of the convertase, thereby affecting convertase-mediated activation of C3; its effect on convertase formation is indirect by impairing C3b deposition [45]. While this distinction may have little impact in some disorders, it is speculated that target selection within the AP may become more critical in diseases like C3 glomerulopathy, where preformed, stable C3 convertases lead to high complement turnover. In such cases, inhibition of existing convertases by targeting Bb, or protection of the C3 substrate by compstatin derivatives, could prove more effective than preventing the formation of new convertases [93].

United we stand — the advent of combination therapies

The trend of combining two or more drugs to enhance the treatment of disorders is gaining momentum across various indication areas. While long established in cancer and infectious disease therapy to mitigate resistance development risks, this strategy is increasingly utilized to leverage additive or synergistic drug effects by harnessing distinct modes of action while minimizing potential adverse events associated with individual drugs. Notable examples include dual antiplatelet therapies for thrombotic event prevention and highly active antiretroviral therapies for HIV infection management. Within current therapies, avacopan is commonly paired with glucocorticoids for treating AAV; indeed, avacopan is primarily seen as a glucocorticoid-sparing adjunct therapy for severe AAV forms [22]. Of course, co-medication may vary depending on disease state, comorbidities, and other factors.

Yet, with an expanding array of complement-targeted drugs and a better understanding of disease mechanisms, combination and add-on therapies also emerge as means to specifically modulate the treatment of complement-related disorders. PNH once again takes center stage in this context. Experimental studies suggest that co-administration of different C3- and/or C5-targeted drugs may be crucial for preventing breakthrough hemolysis in PNH [53, 95]. Alexion's LMW FD inhibitor, danicopan, received specific FDA approval in 2024 as an add-on therapy for patients with inadequate responses to anti-C5 treatment. While C5 blockade attenuates intravascular hemolysis, concurrent inhibition of AP activity at the FD level regulates opsonization associated with extravascular and breakthrough hemolysis risks. A combination of two C5-targeted drugs is currently undergoing phase 3 trials [96, 97]. Cemdisiran, an RNA interference drug that impedes hepatic C5 biosynthesis, was previously assessed as monotherapy in PNH. Despite substantially reducing plasma C5 levels (>90%), the drug failed to adequately control hemolysis, likely due to significant extrahepatic C5 production [98]. Combining cemdisiran with the anti-C5 antibody pozelimab, approved for CHAPLE treatment, enables conservative antibody dosing due to markedly reduced baseline C5 levels. This combination is also being evaluated in a phase 3 trial for gMG [99]. Moreover, modalities that combine activities against different intervention points in a single molecule, such as a fusion protein between an anti-C5 mAb and the regulatory domains of FH (KP104, Kira Pharma) [100], reached clinical development stages.

While combining complement-targeted drugs may enhance established indications like PNH, more profound and transformative impacts may arise from pairing drugs targeting complement, coagulation, and other host defense pathways. In acute and/or thromboinflammatory conditions, inhibiting a single pathway may prove inadequate. Despite complement's clear involvement in conditions like COVID-19, transplant rejection, sepsis, and ischemia-reperfusion injury during stroke or myocardial infarction [101–103], monotherapies with complement therapeutics, antithrombotics, or other pathway-specific interventions typically demonstrated limited therapeutic efficacy. Combining existing drugs with diverse pathway activities or employing broad-spectrum host defense modulators could offer additional avenues to address these unmet medical needs.

Are we there yet? Opportunities beyond low-hanging fruits and beaten paths…

The strides made in treating complement-related disorders are truly transformative, benefiting both the growing number of patients gaining access to increasingly effective and convenient treatment options and the research community, which can rely on clinically validated data. With the therapeutic arsenal rapidly expanding to include a dozen distinct drug entities, one might be tempted to think we have surpassed expectations and that the market is or will soon be saturated. This naturally prompts the

question: "Is there a future in complement-focused drug discovery and development?"

A glance at the pipelines of many pharmaceutical and biotech companies resoundingly affirms that there is indeed a bright future. A multitude of modalities are currently under evaluation in clinical trials, and new experimental modulators are being reported with astonishing frequency [1, 4, 5, 7]. The pharmaceutical industry's leading role in bringing complement-targeted therapeutics to the clinic has been both instrumental and necessary. At the same time, the survey of currently available options reveals certain risk mitigation commonly observed during the shift from "garage band" to mainstream development, including the gravitation towards validated indication fields and established treatment modalities. Indeed, PNH treatments and C5-targeted drugs as the standard-bearers of the initial therapeutic breakthrough [14] still dominate in 2024, and most of the approved drug entities and their targets are traditionally considered "druggable" (i.e. serine protease inhibitors and GPCR antagonists) or pharmaceutically approachable (i.e. mAb; Table 1). Compared with the situation only 5 years ago, however, it is exciting to see that we finally have a panel of inhibitors in the clinic that cover almost all complement activation stages, from initiation to effector functions (Fig. 1).

Although complement is largely perceived as an extracellular defense system, it is increasingly appreciated that the presence of intracellular complement proteins (i.e. complosome) affects cell homeostasis and may shape complement processes in health and disease [104]. Even if known complement-related disease mechanisms can be largely attributed to the system's canonical extracellular functions, there is considerable interest in the development of complosome modulators. But even within the traditional therapeutics realm, there are still some gaps and unmet needs that could or should be addressed. For example, none of the current drugs specifically impair LP activation. Narsoplimab, an mAb inhibiting MASP-2, has completed phase 3 trials for hematopoietic stem cell transplant-associated thrombotic microangiopathy [105, 106], but no positive decision has been made by the FDA. If narsoplimab is approved for this or another clinically evaluated condition, including lupus nephritis, it will likely be the first LP-specific drug to enter the market. Another interesting initiation target is C2, the equivalent to FB of the AP; as C2 is activated by both C1s and MASP-1/2 to form C3 convertases, its inhibition would simultaneously impair CP and LP activity. A C2-directed mAb, empasiprubart, is currently tested in phase 2 trials for multifocal motor neuropathy [107]. Additional strategies to curb CP activation, for example, by preventing C1q binding to antibodies (ANX007, Anoxxon) or interfering with the activity of the C1 complex (RLS-0071), have also advanced in clinical development [108, 109].

While the core components of AP activation and amplification, that is, C3, FB, and FD, are meanwhile covered by specific inhibitors, the exploration of new targets at this stage is shifting toward modulators. Approaches under preclinical and clinical investigation include mAbs against the convertase stabilizer properdin, recombinant forms of physiological AP regulators (e.g. FH, CR1 [102]), and inhibitors of MASP-3, which is involved in the maturation of FD [110]. Within the terminal pathway, available inhibitors so far prevent the activation of C5 or block C5a-mediated signaling. Notwithstanding the auxiliary activity of the C5 inhibitor zilucoplan to destabilize MAC-initiating C5b-6 complexes [44], no complement drug that specifically targets MAC formation is currently approved. Antibodies and other inhibitors against MAC components, in particular, C6 and C7, are in development. Of course, the fact that many targets are covered by approved drugs does not mean that no new developments should be expected. On the contrary, different treatment modalities for the same target may either improve the treatment of established diseases or even open new applications. One source for novel therapeutic modalities that may appear surprising at first glimpse but makes sense when considering the need for pathogens to avoid any complement attack is microbial- and parasite-derived complement inhibitors [111, 112]. Although PK properties and immunogenicity may impose challenges, particularly outside a short-term use in acute disorders, such inhibitors often feature potent activity and intriguing modes of action. Several pathogen-derived complement modulators are in preclinical development, and the tick protein nomacopan (Akari) with dual activity against C5 and leukotriene B4 is clinically evaluated in PNH and other indications [113, 114].

Indication expansion may well be the most critical factor in determining the future of complement-targeted drug discovery and development. While most available drugs are currently approved for one specific indication, either based on pathophysiology or strategic reasons, it is likely that many will venture into new indications in the future. The case of eculizumab impressively demonstrated that such an expansion strategy, partially driven by compassionate or off-label use, can be highly successful. Indeed, most complement therapeutics and clinical candidates are evaluated for more than one indication. Among the diseases for which approval is imminent, or at least seems likely, are C3 glomerulopathy, IgA nephropathy, lupus nephritis, and hematopoietic stem cell transplant-associated thrombotic microangiopathy. As clinicians across various disciplines become increasingly aware of the complement system's role in disease and clinical complications, completely novel indications may appear on the therapeutic radar. This is perhaps best illustrated by the case of CHAPLE, where treatment opportunities were established only a few years after the clinical description of the disease [39, 40]. Although it could appear that many "low-hanging fruits" — indications with highly defined complement pathophysiology and driven by druggable targets — have already been harvested by pharmaceutical companies, there are still opportunities abound. The almost exclusive focus on rare diseases served as a necessary stepping-stone to establishing complement-directed therapeutics but the early clinical and commercial success also distracted from shifting the focus on common conditions and establishing a sustainable long-term strategy beyond orphan markets. The recent progress in the treatment of AMD is a positive step in this direction but needs to be followed by concerted efforts involving partners from research, development, and the clinic. Alongside prevalent autoimmune and inflammatory disorders, ischemic

injury, transplant/biomaterial-related complications, neurological and metabolic diseases present frontiers with promising achievements [2, 4, 9, 115, 116]. Notably, oncotherapy has emerged as another potential key area for complement therapeutics. Rituximab and many other mAb for cancer therapy already engage complement-dependent cytotoxicity as a critical effector arm to facilitate the immune-mediated elimination of cancer cells [117], and considerable effort is currently invested in antibody engineering to improve such effector functions (e.g. HexaBodies [118]). At the same time, the recognition that the complement system plays an important part in shaping the inflammatory microenvironment and overall immune response, the addition of complement inhibitors or engagers to other immune therapy arms such as checkpoint inhibition could open exciting avenues [119].

The implementation of careful clinical diagnostics will not only play a critical role in indication extension but also in patient stratification for clinical trials and therapeutic monitoring. While the assessment of complement-related biomarkers becomes increasingly important, interpreting results is not always straightforward and warrants the collaboration of experts in the field. For example, recent studies have correlated several complement activation markers with the manifestation of Long-COVID syndrome [120–122]. While this could imply that complement is a key contributor to this debilitating and poorly understood condition, thereby opening therapeutic avenues, elevated complement markers may also be an accompanying sign of inflammatory and tissue-damaging processes that drive the disorder. Careful clinical and experimental validation will therefore always be essential when following up on such observations.

Similarly, risk assessment remains an ongoing task that cannot be neglected. Initial and deeply rooted safety concerns, primarily grounded in theoretical considerations and observations from patients with complement deficiencies, have fortunately not been substantiated. Therapeutic complement inhibition has proven relatively safe, even for long-term use in chronic conditions, provided that appropriate precautions such as vaccination and careful patient instruction are implemented [4, 7, 9]. One reason for the better-than-expected risk profile is the redundancy in antimicrobial defense, particularly the increasingly prominent role of adaptive over innate responses throughout life. In various conditions, the detrimental and permanent consequences of inappropriate complement activation may outweigh the partial and situational limitation of defensive functions. Yet, despite the largely favorable risk assessment thus far, it is important to acknowledge that complement inhibition does constitute an intervention in a system with critical roles in defense, homeostasis, and beyond. Bacterial infections remain a risk, with the potential for severe adverse events, as do severe hemolytic crises upon PK or PD breakthroughs. With an increasing number of patients being treated with complement-targeted drugs, the statistical likelihood of expected or new adverse drug events will rise. Similar to the treatment strategy necessitating distinct intervention points, drug modalities, and administration options for each potential complement-related indication, safety assessments must be conducted with equal context awareness. Novel and advanced strategies, including combination therapies or the use of tissue-targeted rather than solution-based inhibitors, may contribute to making complement therapies even more convenient and safe to use. In the latter case, efficient targeting to sites of complement activation can for example be achieved by fusing complement inhibitors to entities that bind opsonins or cell surface markers (e.g. ADX-097, Q32; FH1-5/anti-C3d [123]), by coating cells or material surfaces with regulator-recruiting entities, or by employing the intrinsic recognition capacities of complement regulators [124–126].

When considering the challenges and opportunities discussed in the previous sections, it indeed seems more likely that we are just getting started rather than reaching a plateau. The introduction of additional inhibitors and expansion into new and more prevalent indication areas is expected to benefit patients. Hopefully, it may also improve access to such life-changing treatments, which is often restricted by the high cost of current complement therapies. As in the case of eculizumab [127–129], biosimilars could provide valuable instruments to achieve this goal, especially when patent protection of the second and third wave of complement-targeted therapeutics will expire in a few years. The clinical awareness of complement in disease, the numerous models, diagnostic tests, and research tools established along the way, and the confidence in complement as a targeted platform for therapeutic intervention are expected to propel new endeavors, particularly for academic and clinical researchers and biotech companies. The "fruits" may hang a bit higher and require more effort to be picked, but achieving the next steps along the path may be even more rewarding and foster creativity, insight, and increasing awareness of the complement system's role in disease and therapy.

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Abbreviations: **AAV**: ANCA-associated vasculitis · **aHUS**: atypical hemolytic uremic syndrome · **AMD**: age-related macular degeneration · **ANCA**: antineutrophil cytoplasmic antibody · **AP**: alternative pathway · **BM**: Bruch's membrane · **C3aR**: C3a receptor · **C5aR1**: C5a receptor 1 · **CAD**: cold agglutinin disease · **CHAPLE**: CD55 deficiency with hyperactivation of complement, angiopathic thrombosis, and protein-losing enteropathy · **CP**: classical pathway · **CR1-4**: complement receptor 1–4 · **EC**: endothelial cell · **Epi**: epithelial cell · **FB**: factor B · **FcRn**: neonatal Fc receptor · **FD**: factor D · **FH**: factor H · **GA**: geographic atrophy · **gMG**: generalized myasthenia gravis · **GPCR**: G protein-coupled receptor · **IVH**: intravascular hemolysis · **LMW**: low molecular weight · **LP**: lectin pathway · **MAC**: membrane-attack complex · **MASP**: MBL-associated serine protease · **MBL**: mannose-binding lectin · **NET**: neutrophil extracellular trap · **NMOSD**: neuromyelitis optica system disorders · **PD**: pharmacodynamics · **PK**: pharmacokinetics · **RCA**: regulators of complement activation

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