Compendium of Current Complement Therapeutics

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Abbreviations (for diseases see Table 2): Ab, antibody; AP, alternative pathway; ASO, antisense oligonucleotide; RNAi, ribonucleic acid interference; CP, classical pathway; LP, lectin pathway; FB, factor B; FD, factor D; FH, factor H; FI, factor I; MASP, mannose-associated serine protease 1; PNS, peripheral nervous system; CNS, central nervous system; MAC, membrane attack complex; FDA, The Food and Drug Administration; EMA, European Medicines Agency; SM, small molecule; IV, intravenous; SC, subcutaneous; IVT, intravitreal; Ph, phase; RoA, route of administration; SoC, standard of care; ULN, upper limit of normal; AQP4, Aquaporin-4.

Abstract

The complement system is well known for its role in innate immunity and in maintenance of tissue homeostasis, providing a first line of defence against infection and playing a key role in flagging apoptotic cells and debris for disposal. Unfortunately, complement also contributes to pathogenesis of many diseases, in some cases driving pathology, and in others amplifying or exacerbating the inflammatory and damaging impact of non-complement disease triggers. The driving role of complement in a single disease, paroxysmal nocturnal hemoglobinuria (PNH), provoked the development and eventual FDA (US Food and Drug Administration) approval of eculizumab (Soliris™), an anti-C5 antibody, for therapy. Although PNH is very rare, eculizumab provided clinical validation and demonstrated that inhibiting the complement system was not only well-tolerated, but also provided rapid therapy and saved lives. This clinical validation, together with advances in genetic analyses that demonstrated strong associations between complement and common diseases, drove new drug discovery programmes in both academic laboratories and large pharmaceutical companies. Numerous drugs have entered clinical development and several are in phase 3 trials; however, many have fallen by the wayside. Despite this high attrition rate, crucial lessons have been learnt and hurdles to development have become clear. These insights have driven development of next generation anti-complement drugs designed to avoid pitfalls and facilitate patient access. In this article, we do not set out to provide a text-heavy review of complement therapeutics but instead will simply highlight the targets, modalities and current status of the plethora of drugs approved or in clinical development. With such a fast-moving drug development landscape, such a compendium will inevitably become out-dated; however, we provide a snapshot of the current field and illustrate the increased choice that clinicians might enjoy in the future in selecting the best drug for their application, decisions based not only on efficacy but also cost, mechanistic target, modality and route of delivery.

Complement plays a key role in immune defence and tissue homeostasis

Complement, a key arm of the immune system, is a protein cascade, triggered by specific recognition molecules and progressing through a series of protein/protein interactions that culminates in the formation of a cytolytic pore (Holers, 2014; Merle et al., 2015). Efficient amplification on pathogens ensures an effective response (Harrison, 2018; Lachmann, 2009). Complement proteins are largely generated by the liver and are abundant in plasma (up to 5% total protein), although many are also produced, sometimes exclusively, at extra-hepatic sites (Morgan and Gasque, 1997). The entire cascade progresses from C1 activation through to membrane attack complex (MAC) formation, interactions dictated by *de novo* binding sites revealed following protein conformational changes resulting from proteolytic cleavage of the circulating, native protein (C3, C4, C2, FB, C5) or as a consequence of unfolding (C9) or protein/protein interaction (C6-C9).

The classical pathway (CP) is initiated when antigen-antibody complexes bind the recognition moiety, C1q, triggering activation of the associated proteases, C1r and C1s. Activated C1s cleaves C4 to C4b which binds covalently through its thioester to the target and there captures C2 which is also cleaved by C1s to form the CP C3 convertase C4b2a. **The lectin pathway** (LP) differs from the CP only in the recognition/initiation unit which binds to bacterial sugars, lectins such as mannose binding lectin (MBL), ficolins or collectins. All bind carbohydrate epitopes, triggering activation of the associated proteases MASP1 and MASP2, the latter cleaving C4 and C2 to form C4b2a (Endo et al., 2015; Farrar et al., 2016). C4b2a cleaves C3 to C3b, exposing the internal thioester that covalently binds C3b to surfaces, causing activating surfaces to become densely coated in C3b (opsonised), providing ligands for phagocyte uptake of the target, a crucial defence against infection. C3b also associates with the C3 convertase to create the C5 convertase C4b2a3b.

The alternative pathway is initiated by C3b (generated from the activation pathways or non-specific sources) binding factor B (FB), which is then cleaved by factor D (FD) to form the C3 convertase, C3bBb. C3bBb cleaves C3 to C3b, coating adjacent surfaces and generating a C5 convertase, C3bBbC3b. Tickover activation of C3 in the fluid phase primes the system for rapid amplification on activating surfaces (Harrison, 2018; Lachmann et al., 2018), typified by absence of the regulatory proteins that suppress activation on self cells (Morgan and Meri, 1994). FB can bind to any C3b deposited on an activating surface, including that resulting from activation of the classical and lectin pathways. Thus, the alternative pathway is known as the **amplification loop** of the complement cascade and plays a crucial role in amplifying any small trigger to a large downstream response.

The terminal pathway begins with the capture and cleavage of C5 by either of the C5 convertases, releasing a proinflammatory peptide, C5a. C5b remains attached to the convertase and binds sequentially C6 and C7 and, after release of C5b67 from the convertase and association with membrane, C8 and C9 bind to form the lytic MAC. Recent studies have illustrated the structural complexity of the MAC pore (Hadders et al., 2012; Menny et al., 2018; Serna et al., 2016). Notably, while MAC efficiently lyses aged (or unprotected) erythrocytes and susceptible bacteria, when formed on nucleated self-cells it triggers a plethora of activation events, many of which are highly pro-inflammatory (Triantafilou et al., 2013).

Complement regulatory proteins include plasma proteins factor H (FH) and C4b-binding protein (C4bp) and membrane proteins, CD35, CD46 and CD55 that inhibit the C3/C5 convertases. Control of the enzymes is brought about by decay accelerating activity, characterised by binding of control proteins, such as FH or CD55, to the multimolecular convertases and rapid dissociation of the enzymatic subunit, Bb or C2a. The C3b or C4b that remains is subject to cofactor activity where regulatory proteins bind the remaining subunit, enabling a complement serine protease, factor I (FI) to cleave and inactivate the substrate forming iC3b/C3dg or C4d/C4c. The MAC inhibitor CD59 blocks formation of the lytic pore as soon as C8 is bound to the complex, thus preventing polymerisation of C9. Together these control proteins control complement activation on self-tissues (Holers, 2014; Merle et al., 2015; Morgan and Meri, 1994).

Complement receptors bind the degradation fragments of C3 and C4, providing an additional route for immune defence. The activation fragments C3a and C5a, bind receptors (C3aR/C5aR1/C5aR2) on numerous cell types to trigger diverse responses, ranging from neutrophil recruitment and activation, to priming of endothelial cells to enhance adhesion (Coulthard and Woodruff, 2015; Wetsel, 1995). C5a/C5aR interactions activate the NLRP3 (NOD-, LRR- and pyrin domain-containing 3) inflammasome, impact T cell responses in adaptive immunity and play a multitude of other roles (Arbore and Kemper, 2016; Triantafilou et al., 2013). The receptors CR3 and CR4 on phagocytic cells bind iC3b to promote uptake and clearance of opsonised targets, while C3dg engages CR2 on B cells and follicular dendritic cells (FDCs) to amplify the immune response to opsonised antigens (Carroll and Isenman, 2012; Dempsey et al., 1996). As a consequence of these interactions, complement is intricately entwined in numerous and complex ways with all arms of immunity and host defence (Arbore et al., 2017; Kolev et al., 2014).

Understanding roles of complement in disease fuels drug discovery

Complement dysregulation occurs when the activation and control mechanisms of complement that together play crucial roles in maintaining health and tissue homeostasis fail; when the delicate balance between activation and control is disturbed, tissue damage and disease ensue (Ricklin and Lambris, 2013; Ricklin et al., 2016; Rodriguez de Cordoba et al., 2012). This dysregulation can be a consequence of autoantibodies against regulatory proteins preventing complement control (Brocklebank et al., 2017; Goodship et al., 2012; Paixao-Cavalcante et al., 2012), or gene mutations or polymorphisms in complement proteins leading to altered expression or function (Harris et al., 2012; Heurich et al., 2011; Rodriguez de Cordoba et al., 2012). Autoantibodies against tissue antigens can also drive inappropriate complement activation and damaged tissue drives further activation and dysregulation in a vicious cycle of inflammation and tissue damage.

Complement involvement in disease has been recognised for more than 50 years, particularly in diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) (Schur and Austen, 1968) (see **Table 1** for all disease abbreviations). Despite this recognition, there was some resistance to therapeutic targeting of the system based on concern that blocking a crucial arm of innate immunity would be unsafe (Harris, 2018). The demonstration that MAC caused haemolysis in the ultra-rare disease paroxysmal nocturnal hemoglobinuria (PNH) broke this resistance and led to the development of the blockbuster MAC-blocking anti-C5 drug, eculizumab (Rosse and Dacie, 1966). Eculizumab, a game-changer therapy, was approved by the Food and Drug Administration (FDA) for treatment of PNH in 2007, some 40 years after the recognition that complement caused this devastating disease (Rother et al., 2007). Approval of eculizumab for PNH therapy brought much needed clinical validation and demonstrated that blockade of complement could be achieved relatively safely and bring about profound and life-changing results. Eculizumab was the first drug to be approved that blocked the complement pathway completely at a specific point, the only other complement drugs currently approved for therapy have been replacement therapies for C1inh (Berinert, Cinryze, Ruconest) in hereditary angioedema (HAE) where C1inh deficiency causes dysregulation of the complement and kinin systems (Csuka et al., 2017; Morgan, 2010). The slow progress along the road to approval for anti-complement drugs evidences the complexities of successful drug development for inhibition of an abundant and important effector system; many of the barriers to progress remain today.

Common complement driven diseases really came to prominence in 2005 when frequent polymorphisms in FH were shown to dictate risk for the common blinding disease, age-related

macular degeneration (AMD) (Hageman et al., 2005; Haines et al., 2005; Klein et al., 2005). At that time, eculizumab was proving successful in clinical trials for PNH and the suggestion that complement dysregulation was driving this common blinding disease triggered an explosion of interest, with numerous biotechnology and pharmaceutical companies initiating anti-complement drug discovery programmes. FDA approval for eculizumab in the rare renal disease atypical haemolytic uremic syndrome (aHUS) in 2011 fuelled this frenzy, with a procession of new drugs in development and clinical trials over the last few years (Brodsky et al., 2008; Harris et al., 2018; Morgan and Harris, 2015; Ricklin et al., 2018). Not surprisingly, the focus for these new drugs has remained PNH and aHUS, diseases where complement is the primary driver of disease and in which complement inhibition has been validated (Harris et al., 2018). The list of diseases (illustrated in **Figure 1**) has expanded to include AMD and many other pathologies where complement is known to play a role. These include generalised myasthenia gravis (gMG) where eculizumab was approved by FDA and European regulators in 2017 and Neuromyelitis optica spectrum disorder (NMOSD), which was approved by the FDA in June 2019.

The success of eculizumab in the treatment of PNH and aHUS demonstrates that the terminal pathway is the driving force that damages and/or activates the target cells in these rare diseases. The tissues inappropriately under attack, respectively blood cells, particularly erythrocytes, and endothelial cells, are readily accessible to the drug as they are exposed to plasma; thus, it is perhaps not surprising that these diseases can be effectively treated using systemic C5 blockade. Many other diseases are driven by complement dysregulation, as illustrated in **Figure 1**. These include the renal disease C3 glomerulopathy (C3G), the neurological disease NMOSD, the neuromuscular disease gMG and the blinding disease AMD; all are target indications for a growing number of anti-complement drugs. The evidence for other diseases is rapidly building and a strong case can be made for anti-complement therapies in diverse diseases, including iatrogenic and surgery-related conditions. Increased levels of complement biomarkers in plasma and disease-relevant fluids, such as synovial fluid and cerebrospinal fluid, or complement deposition in tissues, indicate that complement is abnormally activated, although whether this is cause or effect of disease may need further investigation. Genetic associations with disease, positive readouts from animal models and evidence from clinical studies all combine to support a role of complement in pathogenesis and validate specific diseases as targets for therapy (Harris et al., 2018; Ricklin and Lambris, 2013; Ricklin et al., 2016).

Challenges, pitfalls and risks associated with blockade of a key arm of innate immunity accompany this growth in the scope of anti-complement therapies (Harris, 2018). For example, opsonisation and bacteriolytic activity can be severely compromised, increasing risk of infection (Socie et al., 2019). Additionally, for most complement proteins, target concentration is high, necessitating huge doses of drug, particularly if an individual is in the acute phase of an illness or injury that further increases plasma levels of many complement proteins. Tissue damage may be mediated by locally produced complement, rather than systemic complement, meaning that tissue access of the drug is critical. These factors, together with the wide normal ranges of target proteins found in the general population, mean that complement blockade, and particularly the optimal goal for many diseases of modulating complement rather than completely blocking, is challenging. New ways to overcome these challenges are emerging with next generation drugs progressing through clinical trials as described below.

The aim of this article is neither to review complement and disease nor the drug development process; many outstanding recent reviews cover these areas and are cited above. Rather we will provide a snapshot of the current status of the field, highlighting those drugs which are in clinical development or approved, and next generation approaches bringing forward new complement targets, applications, modalities and routes of administration (**Table 2**).

Next generation drugs

Eculizumab has proven very effective in PNH and aHUS; why then are so many of the new drugs entering clinical development also targeting these diseases, often even targeting the same element of the complement system? The answer is, of course, that it is a safe bet. Approval of eculizumab was a major milestone for the field, providing long-sought clinical validation for complement inhibition in man. There are, however, drawbacks associated with this drug, including high cost, risk of meningococcal infection, frequency and amount of dosing, route of administration and difficult pharmacokinetics as the target C5 can increase in concentration under conditions of acute phase, resulting in break-through symptoms. There are also clinical issues with the use of eculizumab; indeed, in PNH, while major life-threatening complications, such as thrombotic events, are well-treated, a substantial proportion of patients remain transfusion-dependent on eculizumab (Hillmen et al., 2013). PNH erythrocytes lack CD55 (decay accelerator) as well as CD59 (MAC blocker), therefore complement continues to amplify. As the cells are no longer removed from the circulation by MAC mediated lysis, they accumulate activated C3 on their surfaces and are subject to haemolysis

due to phagocytic uptake in the extravascular space (Risitano et al., 2009). Problems such as these, together with the ambition to expand the number of indications treated with anti-complement drugs, have driven the development landscape illustrated in **Table 3** and **Figure 2**. Novel and innovative ways of inhibiting complement that move beyond C5 and ultra-rare diseases and circumvent the challenges associated with complement inhibition are evolving; these second generation high-potential drugs are rapidly progressing through phase 2 clinical trials and are likely to challenge eculizumab and change the field in the near future (**Figure 3**). Both drugs targeting C5 (in ways that differentiate from eculizumab) and therapeutics targeting other components and pathways of complement are progressing through clinical development. Indeed, a next-generation 'recycling' form of eculizumab, termed ravulizumab (Ultomiris™) (Sheridan et al., 2018), has been FDA- and EMA-approved for PNH, is under fast-track review for aHUS and is competing phase 3 trials in gMG; however, no other new drugs have yet made it past phase 3.

Innovations in next generation drugs are wide and varied. Recycling or 'pH-switched' antibodies can be generated from existing antibodies by modifying the antigen-binding region, frequently by incorporating histidine residues, such that the antibody while retaining high affinity for target at pH 7.4, loses affinity in the acidic pH 6.0 environment of the endosome (below the isoelectric point of histidine). When antibody is passively internalised into endothelial cells, the pH drop in the endosome results in disengagement of the target and recycling of the 'empty' antibody back to the circulation (Igawa et al., 2010). This process improves the pharmacokinetic properties of the drug, enabling less frequent dosing. Ravulizumab, the next generation 'recycling' form of eculizumab, is administered in PNH every 8 weeks, rather than every 2 weeks, although the dose is much higher (3.3 g IV contrasting to 0.9 g IV for eculizumab), a negligible saving on overall drug dose! Another recycling anti-C5 antibody is currently in phase 2 development, crovalimab (Roche; SKY59); this antibody was selected during the original screening process for its recycling or pH-switched properties (Fukuzawa et al., 2017; Sampei et al., 2018). Crovalimab is being developed as a SC-administered agent and dosing schedules in reported trials suggest that a lower dose (340 mg every two weeks) was effective (Risitano et al., 2019). Crovalimab is also effective in patients carrying the R885H C5 variant (common in Japan), resistant to eculizumab inhibition. A different approach to decrease drug dose is to develop an agent that binds neoepitopes on complement proteins rather than targeting the native protein. Various drugs are in clinical development, including IFX-1 (InflaRx), which binds the released C5a fragment (Riedemann et al., 2017), and the preclinical antibody, BIVV020 (Sanofi), reported as binding activated C1s.

Route of administration is a critical consideration. The move from IV administration to SC or even oral administration has been rapidly progressing. As well as crovalimab, noted above, several peptide-based anti-complement drugs are being administered SC, including APL-2 (C3 inhibitor; Apellis), AMY101 (C3 inhibitor; Amyndas) and zilucoplan (C5 inhibitor; RaPharma). Some small biologics, such as nomacopan (C5 inhibitor; Akari), are also administered SC, and various strategic partnerships announced in company press releases in recent times (for example, Zealand Pharma and Alexion) reveal an expanding pipeline of SC drugs. Avacopan (Chemocentryx), an orally active inhibitor of C5aR1, is in phase 3 for antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) and in phase 2 for a number of other indications (Table 3) (Bekker et al., 2016). Other orally bioavailable drugs are progressing through phase 2 with a focus on the amplification loop. LNP023 (Novartis) blocks FB and is in clinical trials (oral route twice daily) for a number of indications including PNH and renal disease (Schubart et al., 2019). Achillion's SM FD inhibitors are also being tested in these indications, although the target has a very high synthesis rate (1.33 mg/kg/day) (Pascual et al., 1988), necessitating thrice daily oral administration. Other oral drugs are in preclinical development, including RaPharma's SM targeting C5. Such orally-bioavailable SM drugs, including targets within the amplification loop and C5, are likely to change the landscape of complement drug development in the years to come. While the required dosing may be frequent, due to target concentration or turnover, the oral route and ability to rapidly reverse inhibition by stopping treatment in the face of infection or other complication may be of huge benefit.

Targeting at the nucleotide level offers a different approach to overcome the challenge of high target concentration and drug dose, the goal is to prevent translation of the protein and thus its release to the blood stream. Alnylam and Ionis have led the way with, respectively, C5 RNAi (ribonucleic acid interference; cemdisiran) and FB antisense oligonucleotide (ASO), both in phase 2, the former for IgA nephropathy (IgAN) and the latter for AMD (Grossman et al., 2017; Kusner et al., 2019). Cemdisiran was originally trialled in PNH and although it successfully blocked synthesis of C5 to 98% the trace residual C5, possibly generated extra-hepatically, resulted in some lysis with lactate dehydrogenase (LDH) ~ 1.5 times upper limit of normal (ULN; press release December 5th 2016). Generation of complement components by tissues outside of the liver, such as FD by adipocytes, C7, C1q and properdin by cells of monocytic lineage, can limit utility of this liver-targeting approach. Many tissues, including the central nervous system (CNS) and the joint can generate all components of the complement cascade, particularly when cells are under the influence of inflammatory cytokines. Even when the liver contributes the majority of a specific protein, local biosynthesis may be the driver of disease or pathology, for example in kidney transplant (Farrar et al., 2006; Pratt et al., 2002); this may stymie anti-sense approaches targeting hepatic synthesis.

Local and 'targeted' inhibition of complement has been the driver behind a number of innovative drugs which deliver therapy to tissues; various targeting moieties have been reported, some of which bind C3 fragments and others that bind epitopes exposed on damaged tissues (Holers et al., 2013; Holers et al., 2016; Ruseva et al., 2015). TT30, initially developed by Taligen Therapeutics and taken through phase 1 testing by Alexion in PNH (Fridkis-Hareli et al., 2011), is a chimeric molecule, with one arm binding complement activation fragments in tissues, and the second arm comprising the complement regulator domain, here the amino-terminal portion of FH. This agent homes to the tissue under attack, delivering lasting therapy, while excess agent is excreted or metabolised. Such agents have several advantages, not only should they decrease dose of drug as they target activated complement, not native proteins, but they should also lower risk of infection as systemic inhibition is transient. TT30 has not progressed beyond phase 1 but various similar agents remain in preclinical development. A number of companies have reported development of gene therapy-based agents for treatment of AMD (for example, Gyroscope Therapeutics https://gyroscopetx.com/; Gemini Therapeutics https://www.geminitherapeutics.com/), with exciting potential for local therapy, but the nature of these drugs and their targets are not disclosed.

Crossing barriers presents a particular problem for CNS diseases; to date, none of the drugs in development has been selected for capacity to cross the blood-brain barrier (BBB) and access the CNS; given that complement has been implicated in a number of CNS disorders, this is a major unmet need (Carpanini et al., 2019). It is possible, although difficult, expensive and risky, to inject or infuse drugs directly into the intraventricular or intrathecal space. Thus, a number of approaches for crossing the BBB are in development; these include the 'trojan horse' method of piggy-backing drugs onto peptides or antibodies that target receptors, such as the transferrin receptor or insulin receptor. These delivery methods are reviewed extensively elsewhere (Abdul Razzak et al., 2019; Carpanini et al., 2019). Although not a complement target, gene therapy targeting motor neurons was approved by the FDA in 2019 for treatment of spinal muscular atrophy in children (Zolgensma™) illustrating the potential for gene therapy in the CNS. This drug utilises a non-replicating adeno-associated virus (AAV9) vector that can cross the BBB to deliver the target gene. In a recent press release (July 18, 2019), Apellis announced the development of APL-9, a PEGylated C3-inhibiting peptide designed to prevent rapid complement-mediated attack on AAV-based vectors and improve efficacy of gene therapy.

Selecting and stratifying diseases and individual patients for complement interventions will be challenging as the field expands beyond the ultra-rare complement-driven conditions. First, it will be

necessary to demonstrate that complement activation is occurring in the candidate disease; second it is important to consider heterogeneity – that some patients with a particular disease label may have a highly complement driven disease while others will not; interventions can only work in the former group. As an example, multiple sclerosis, although typified by CNS myelin loss and resultant functional deficits, encompasses a spectrum of disease types; pathological studies have shown that complement deposits in brain are a major feature in about a third of cases (Lucchinetti et al., 2000). Similarly, with the focus of anti-complement therapy in renal disease, attention has focussed in recent years on treatment of the devastating renal disease, C3G, for which there is no FDA-approved therapy. Unlike in aHUS, it is thought that C3 dysregulation dominates in the fluid phase in C3G, with dysregulation of surface-bound C5 convertase in a subset of patients. Case reports, and a small clinical trial in the US (six patients) using eculizumab to treat C3G, describe some improvement in a subset of patients (Lebreton et al., 2017; Nester and Smith, 2016). Limited data on a heterogeneous disease make therapeutic evaluation difficult, but improvement in renal function may correlate with high plasma terminal complement complex (TCC) levels pre-treatment and evidence of rapidly progressive or acute crescentic disease (Le Quintrec et al., 2015). Recent guidance from NHS England supports use of eculizumab in a tightly stratified group of post-transplant patients with evidence of acute inflammation and disease recurrence on kidney biopsy. Stratification and selection will be particularly important for clinical trials, including only those patients with evidence of complement dysregulation. Stratification can be based on complement activation biomarkers, particularly activation fragments and complexes, in plasma or other biological fluids, as recently described for predicting progression in Alzheimer's disease (Hakobyan et al., 2016).

How much inhibition is enough is an important and unanswered question that will need to be addressed as complement therapeutics become more widely used. In this context, PNH, the first disease target, is unique in that complete inhibition of MAC formation is essential; PNH erythrocytes are devoid of complement regulators and even a small amount of free C5 in eculizumab treated patients is sufficient to cause breakthrough haemolysis (Kelly et al., 2008). In most other disease situations, turning down rather than turning off complement is likely to be sufficient to confer therapeutic effect. The aim of treatment would be to reverse dysregulation and restore homeostasis. In this context, the amplification loop represents an excellent target. Reducing cycling through the amplification loop by increasing loop regulation or reducing availability of convertase could enable fine-tuning of therapy to ameliorate pathology while retaining the protective roles of complement in immune defence. This will be a significant advantage for treating common diseases in elderly and infection-vulnerable individuals in the community. Several AP-specific drugs are in

phase 2 development, including inhibitors of FB and FD. Other drugs which have modulatory properties are on the horizon; homing agents described above which deliver functional domains of regulators such as FH can directly modulate the convertase enzymes, as can the preclinical molecule AMY201 (Amyndas), a truncated, recombinant form of FH engineered to bind with superior efficacy to target surfaces. Gene therapies designed to boost the tissue's ability to control complement at disease sites have exciting potential to modulate. Finally, it may be possible to block natural modifiers of complement; properdin stabilises the AP convertase enzymes and MASP3 activates FD, interference at these levels using drugs such as CLG561 (anti-properdin, Novartis) or OMS906 (preclinical anti-MASP3, Omeros) may nudge the complement system towards restored homeostasis. Importantly, anti-properdin in animal models can have beneficial or detrimental effects depending on the disease, highlighting the absolute requirement for full understanding of disease mechanism and appropriate patient stratification in order to get the right drug into the right patient at the right time (Ruseva et al., 2012; Ueda et al., 2018).

Concluding remarks

This article has sought to provide a snapshot of the anti-complement drug landscape at the time of writing. The landscape is complex and fast moving, so inevitably, there will be changes even by the time that this is published. Nevertheless, we suggest that the Compendium captures the complexities and direction of travel of the field and illustrates the trends and assumptions that have shaped the field to date.

In the twelve years since the approval of eculizumab for PNH, overnight transforming complement inhibition from an archaic interest in animal models to a clinically tractable target in human disease, there has been considerable activity, with many companies, large and small, launching complement programmes and complement-targeted drugs; however, progress to clinical use has been disappointing. Apart from eculizumab, its successor ravulizumab and various takes on the venerable C1inh, nothing new has been approved, although intense activity in clinical trial phases 2 and 3 predicts rapid change in the clinical toolbox in the near future. The recent extension of Alexion's key patents in the US for eculizumab through to 2027 (press release August 15th 2017) may inhibit challengers in the C5 mAb space but other approaches to complement inhibition may, perversely, be prioritised and accelerated.

Looking back, the view is more battlefield than landscape, littered with the corpses of abandoned or failed drugs. In part, this carnage is a result of an over-conservative "me too" approach that has

focussed on the very areas in which eculizumab has been successful – targeting C5 in PNH and other ultra-rare diseases; many of the survivors have sought to diversify in terms of complement targets and, to some extent, disease targets. Nevertheless, most remain focussed on ultra-rare or rare diseases. The exception to date has been AMD, a relatively common disease where the genetics made the case for testing anti-complement drugs. Although local (intravitreal) therapies have predominated to date, systemic approaches are also being explored; these may lay the foundations for anti-complement drugs in other common and chronic complement dysregulation diseases where there is considerable unmet need.

Looking forward, there is every reason to be optimistic. There is intense activity, many new Pharma entrants to the area, a broadening of disease focus and a growing enthusiasm to move beyond C5 with some innovative approaches that may reduce costs and address safety issues. Belatedly, the field has realised that for most complement dysregulation diseases – perhaps all except PNH – the aim should be to reduce not eliminate complement activation in order to restore homeostasis. This should be low risk, particularly with regard to bacterial infections, and may open the door to orally active agents that will revolutionise the field. Our expectation is for continued rapid progress and a landscape that will, in just a few years, have changed beyond recognition.

Figure Legends

Figure 1. Complement activation is implicated in numerous diseases. Complement exists in a delicate balance between activation and regulation. When that balance becomes disturbed, tissue can be damaged and disease ensues. Complement is implicated in many different diseases although in many cases it acts to exacerbate a cycle of inflammation induced by other triggers or causes; anti-complement therapy may have a role to play in treatment of these diseases. In some cases, such as PNH, aHGUS and C3G, complement is the main driver of disease. These diseases are more prevalent in clinical trial and are are indicated in red in the figure. Anti-complement therapy is thought to play a key role in the treatment of these diseases. Refer to Table 1 for all disease abbreviations. Cartoons from PRESENTERMEDIA (www.presentermedia.com).

Figure 2. Anti-complement drugs currently in clinical development. The concentric rings indicate the different phases of clinical development, with 'approved' in the centre. Only drugs currently in clinical development are shown and the most advanced stage of development for any indication is

shown; trials posted but not yet recruiting are included. Colouring and shape indicate modality and route of administration. There are a number of drugs in clinical development, indicated as preclinical or first-time-in-human on company websites (Gyroscope Therapeutics, Gemini Therapeutics and others), these are only included in this diagram if **targets** have been disclosed. The inclusion of C1inh drugs in this figure reflects their repurposing for complement-mediated complications of kidney transplant.

Figure 3. Development of next generation drugs.

The pyramid indicates the potential path of travel for 'next generation' anti-complement drugs. Early drugs have been dosed at high levels, often intravenously, with the aim to totally block the pathway. Later drugs have longer duration of action and/or can be administered subcutaneously or orally. Some drugs in, or approaching, clinical development may have the capacity to modulate the system rather than turn it off altogether. The potential to localise therapy to the tissue in need using gene therapy or 'homing' agents presents exciting possibilities. Towards the pinnacle of the pyramid lie future drugs, currenty speculation; drugs which can cross the blood brain barrier (BBB) or other obstacles, that can reverse dysregulationand restore homeostasis, or that can modulate disease outcome by impacting other arms of the immune system or other biological cascades. Cartoons from PRESENTERMEDIA (www.presentermedia.com)

Table 1. Abbreviations used for diseases in text, tables and figures.

Table 2. Compendium of drugs in development 2019. **(a)** This table lists all anti-complement drugs in clinical development (to the best of our knowledge). For current stage of development for different indications please refer to table 3. C1inh drugs (Cinryze, Berinert, Ruconest) have previously been reported for HAE, their inclusion in this table reflects their repurposing for complement-mediated complications of kidney transplant. Unless otherwise indicated the drug blocks the function of the target; other kinds of activity are noted under 'additional information'. **(b)** Drugs in preclinical development, only drugs where the target has been disclosed are included. Route of administration is not included for preclinical assets. For disease abbreviations refer to Table 1. IV, intravenous; SC, subcutaneous; IVT, intravitreal, Ab, antibody; RNAi, ribonucleic acid interference; ASO, antisense oligonucleotide; SM, small molecule; ULN, upper limit of normal; AQP4, Aquaporin-4.

Table 3. Drugs in current clinical trial. Each line represents an ongoing clinical and these are shaded according to the phase of development. Only company-sponsored trials are indicated and completed trials are excluded. Red text indicates that a drug has already been approved for treatment of a different indication and is being trialled for a new purpose. For disease abbreviations refer to Table 1. For modality and route of administration please refer to Table 2. HV; healthy volunteer.

* Recently approved by FDA for NMOSD, June 2019

Conflicts of interest

Newcastle University has received payment for participation of CLH at company Scientific Advisory Boards and as a consultant to pharmaceutical companies. CLH has research collaborations with pharmaceutical companies and is a prior employee of GlaxoSmithKline but has no shares/options. BPM has provided advice on complement to Roche and is a consultant to GlaxoSmithKline; all fees are paid to Cardiff University. Other authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Table 1. Abbreviations used for diseases in text, tables and figures.

Abbreviation	Disease
AAV	Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis
AD	Alzheimer's disease
aHUS	Atypical hemolytic uremic syndrome
AKI	Acute kidney injury
AMD	Age-related macular degeneration
AMR	Antibody-mediated rejection
APS	Antiphospholipid syndrome
ARDS	Acute respiratory distress syndrome
BD	Berger's disease
BP	Bullous pemphigoid
C3G	C3 glomerulopathy
C3GN	C3 glomerulonephritis
CAD	Cold agglutinin disease
COPD	Chronic obstructive pulmonary disease
CPB	Cardiopulmonary bypass
DDD	Dense deposit disease
DGF	Delayed graft function
GA	Geographic atrophy
GBS	Guillain-Barré syndrome
gMG	Generalized myasthenia gravis
GPA	Granulomatosis with polyangiitis
GVHD	Graft versus host disease
HAE	Hereditary angioedema
HS	Hidradenitis suppurativa
HSCT-TMA	Hematopoietic stem cell transplant-related thrombotic microangiopathy
IgAN	IgA nephropathy
I/R	Ischemia/reperfusion
IC-MPGN	Immune complex-mediated membranoproliferative glomerulonephritis
IMNM	Immune Mediated Necrotizing Myopathy
IPCV	Idiopathic polypoidal choroidal vasculopathy
KT	Kidney transplant
LN	Lupus nephritis
MN	Membranous nephropathy
MPA	Microscopic polyangiitis
MS	Multiple sclerosis
NMO (NMOSD)	Neuromyelitis optica (spectrum disorder)
PG	Pyoderma Gangrenosum
PNH	Paroxysmal nocturnal hemoglobinuria
RA/OA	Rheumatoid arthritis/Osteoarthritis
SIRS	Systemic inflammatory response syndrome
SLE	Systemic lupus erythematosus
STGD1	Stargardt Disease 1
SVS, SS	Severe sepsis, septic shock
TMA	Thrombotic microangiopathy
wAIHA	Warm type autoimmune hemolytic anemia

wAMD	Wet AMD

Table 2. Compendium of drugs in development 2019

(a) This table lists all anti-complement drugs in clinical development (to the best of our knowledge). For stage of development for different indications please refer to table 3. C1inh drugs (Conryze, Berinert, Ruconest) have previously been reported for HAE, their inclusion in this table reflects their repurposing for complement-mediated complications of kidney transplant. Unless otherwise indicated the drug blocks the function of the target; other kinds of activity are noted under 'additional information'. For disease abbreviations refer to Table 1. IV, intravenous; SC, subcutaneous; IVT, intravitreal, Ab, antibody; RNAi, ribonucleic acid,interference; ASO, antisense oligonucleotide; SM, small molecule; ; ULN, upper limit of normal; AQP4, Aquaporin-4.

DRUGS IN CLINICAL DEVELOPMENT OR APPROVED						
Drug name	Alternative names	Company	Target	Modality	Route of administration	Additional information
CLASSICAL PATHWAY						
Cinryze		Takeda Pharmaceuticals (Originator Shire, Takeda 2019)	C1r/s; MASPs	Purified native protein	IV; Ph3 trials for SC dosing completed (NCT02316353, NCT02584959)	Plasma derived protein; controls both complement and contact systems. Physiological inhibitor of lectin and classical pathways, prevents activation of C1r/s and the MASPs. Originally approved for HAE, now in trial for complications of kidney transplant.

Abbreviations (for diseases see Table 2): Ab, antibody; AP, alternative pathway; ASO, antisense oligonucleotide; RNAi, ribonucleic acid interference; CP, classical pathway; LP, lectin pathway; FB, factor B; FD, factor D; FH, factor H; FI, factor I; MASP, mannose-associated serine protease 1; PNS, peripheral nervous system; CNS, central nervous system; MAC, membrane attack complex; FDA, The Food and Drug Administration; EMA, European Medicines Agency; SM, small molecule; IV, intravenous; SC, subcutaneous; IVT, intravitreal; Ph, phase; RoA, route of administration; SoC, standard of care; ULN, upper limit of normal; AQP4, Aquaporin-4.

Berinert		CSL Behring	C1r/s; MASPs	Purified native protein	IV	As above.
Ruconest		Pharming	C1r/s; MASPs	Biologic	IV	Recombinant C1inh, produced in transgenic rabbits (milk). Originally approved for HAE, now in trial for complications of kidney transplant.
Sutimlimab	TNT009 BIVV009	Sanofi (Originator True North; Bioverativ 2017; Sanofi 2018)	C1s	Ab	IV	Showed improvement in haemolytic events in CAD (Ph1b).
LECTIN PATHWAY						
Narsoplimab	OMS721	Omeros	MASP2	Ab	IV; IV loading, daily SC maintenance in trial (NCT03205995)	Ph2 in IgAN reports improved proteinuria in patients with and without concomitant steroid therapy. Those on steroids at time of enrolment were able to reduce or stop steroids. Breakthrough therapy designation granted by FDA for IgAN and for high-risk HSCT-TMA.
ALTERNATIVE PATHWAY/AMPLIFICATION LOOP/COMPLEMENT C3						
Danicopan	ACH-0144471 ACH-4471	Achillion	FD	SM	Oral	Ph2 data from combination trial with eculizumab (in patients with transfusion-dependent anemia) demonstrated potential to improve

						anemia and decrease transfusions (press release May 17, 2019). Enrolment milestone reached in Ph2 C3G (April 2019), 6 month (blinded) and 12 month (open label). Ph2 proof-of-mechanism in C3G reported positive biomarker data (C3 & Bb levels) and improved renal function (November, 2017).
ACH-5228		Achillion	FD	SM	Oral	Reported as 'next generation' drug with improved potency and pharmacokinetic properties allowing for reduced frequency of dosing. Ph1 data indicate 120 mg twice daily supressed activity of the AP >95% (press release July 22, 2019).
ACH-5448		Achillion	FD	SM	Oral	Reported as 'next generation' drug with improved potency and pharmacokinetic properties allowing for reduced frequency of dosing.
IONIS-FB-L_{RX}		Ionis Pharma (Partnership with Roche)	FB	ASO	SC	LICA technology; blocks (liver) expression of FB. Ph1 reported dose-dependent reductions in FB and a positive safety and tolerability profile.
CLG561	NOV-7	Novartis (Morphosys Ab; originator Alcon Novartis spun off	Properdin	Ab	IVT	Ph2 in GA, combination with Tesidolumab. Data demonstrated no significant impact on change in GA lesion size.

		Alcon 2019)				
LPN023		Novartis	FB	SM	Oral	Binds the active site of FB and thus inhibits the convertase and C3 cleavage.
APL-2	Pegcetacoplan (Derivative of compstatin)	Apellis (Original molecule (POT-4), Potentia Pharmaceuticals; Alcon 2009; Apellis 2010)	C3	Peptide	SC other than GA which is IVT	POT-4 (APL-1) is a derivative of compstatin; APL-2 is a PEGylated derivative. Ph3, head-to-head with eculizumab completed enrolment. Ph2 in PNH reported normalization of markers of intravascular and extravascular hemolysis. Patients in Ph2 CAD/wAIHA showed improvement in hematologic measures and in quality of life scores, particularly in CAD.
APL-9		Apellis	C3	Peptide	IV	Cyclic peptide with same target and mode of action as APL-2; smaller mass and shorter half-life. Developed to inhibit host response to AAV vectors in gene therapy.
AMY-101	Cp40; Derivative of compstatin	Amyndas	C3	Peptide	SC; IV; administered weekly to interproximal papilla in Ph2 trial for gingivitis.	Compstatin derivative with much improved potency compared to original molecule (Qu et al., 2013). In Ph1, administered SC every 48 hours and maintained effective C3 blockade with a satisfactory safety profile.

Mirococept	APT070	King's College London, MRC	Functional domains of CR1 targeted to endothelium via lipid 'tail'	Biologic	Perfused through the kidney prior to transplant. EMPIRIKAL trial.	Inhibits both CP and AP C3 convertase. Based on a natural convertase regulator, comprises a fragment of CR1 and possesses decay and cofactor activity (Mossakowska et al., 1999; Smith, 2002).
COMPLEMENT C5						
Eculizumab	Soliris	Alexion	C5	Ab	IV	Approved for PNH, aHUS. Approved gMG (FDA, October 2017; EMA August 2017). Approved by FDA for NMOSD (anti-AQP4+ve), June 2019.
Tesidolumab	LFG316 NOV-4	Novartis (Morphosys Ab; originator Alcon)	C5	Ab	IV IVT	In GA, LFG316 did not reduce lesion growth or improve visual acuity.
Pozelimab	REGN3918	Regeneron	C5	Ab	IV & SC	Regeneron and Alnylam are collaborating with combination therapy Pozelimab/Cemdisiran. Ph1 HV completed 2018. Ph1 in PNH reported on company pages.
Crovalimab	RG6107 RO7112689 SKY59	Roche (Originator Chugai Pharmaceuticals)	C5	Ab (recycling)	IV and SC formulations tested	Recycling 'pH switched' antibody leading to reduced dosing (340 mg SC every 2 weeks appears effective) (Risitano et al., 2019). Effective in patients carrying the R885H

						C5 variant.
Ravulizumab	ALXN 1210 ULTOMIRIS	Alexion	C5	Ab (recycling)	IV	Recycling or 'pH switched' antibody leading to reduced dosing. Ultomiris administered IV every 8 weeks, Soliris is administered IV every 2 weeks. Approved for use in adult PNH by FDA (December 2018) and EMA (July 2019). Supplemental biologics license application (sBLA) under priority review for treatment of aHUS (June 2019). Ph3 trial of SC formulation expected.
ABP 959		Amgen	C5	Ab (Biosimilar)	IV	Eculziumab biosimilar; note eculizumab patent extension to 2027 (Alexion press release August 15th, 2017).
Zilucoplan	RA101495	RaPharma	C5	Peptide	SC	Positive date reported from Ph2 in gMG (December, 2018) and Ph2 in PNH (February, 2018).
Zimura	ARC 1905	IVERIC bio (Changed name from Ophthotech Corp to IVERIC bio in April 2019 as transitioned to gene therapy company)	C5	Aptamer	IVT	Ph2 combination with Lucentis proved to be safe but is not being developed further (press release, Nov 2018).

Nomacopan	rVA576 Coversin	Akari	C5	Biologic	SC Topical (in AK)	Recombinant form of tick protein OmCI (Ornithodoros moubata complement inhibitor). Also inhibits leukotriene pathway (LTB4). Effective in patients carrying the R885H C5 variant. Ph2 in PNH achieved primary endpoint, defined as a reduction in LDH to ≤1.8 times ULN. Ph2 aHUS reported to be on hold in expectation of Q4 2019 trial in pediatric HSCT-TMA. Early safety and efficacy data in AKC Ph1 (topical) were positive (June 19, 2019). Initial Ph2 data in BP demonstrated clinical efficacy (3 patients reported).
Cemdisiran	ALN-CC5	Alnylam	C5	RNAi	SC	Blocks (liver) expression of C5. Originally tested in PNH; despite effective reduction in circulating C5 levels, some circulating C5 was detectable and LDH levels were ~1.5 times ULN.
COMPLEMENT C5a/C5aR1						
Avacopan	CCX168	Chemocentryx (Vifor Pharma has rights to	C5aR1	SM	Oral	In Ph2 for AAV, avacopan provided effective control of the disease while allowing elimination of high-dose

		commercialize in Asia, including Japan and the Middle-East)				steroids. Ph2 in IgAN completed, improved proteinuria reported at 12 weeks.
IFX-1		InflaRx	C5a	Ab	IV	Binds C5a but not the native C5 protein. Development in SIRS and sepsis on hold. Ph2 SHINE study in HS did not meet primary endpoint although post-hoc data analysis suggested robust anti-inflammatory activity; development continues (press release July 18th 2019).
MAC (C6-C9)						
AAVCAGsCD59	HMR59	Hemera Biosciences	Expression of soluble CD59	Gene therapy	IVT	Gene therapy, expression of soluble CD59 in the retina. CD59 is a natural regulator of MAC formation.

Table 2 (b) Drugs in preclinical development, only drugs where the target has been disclosed are included. Route of administration is not included for preclinical assets.

DRUGS IN PRECLINICAL DEVELOPMENT			
Drug name	Company	Target	Modality
Name not disclosed	RaPharma	FD	Peptide
OMS906	Omeros	MASP3	Ab
BIVV020	Sanofi	activated C1s	Ab
Name not disclosed	RaPharma	C1s	Peptide
AMY-201, 'mini-factor H'	Amyndas	Contains functional domains of FH; complement modulator	Biologic
PRO-02	Prothix BV	C2	Ab
IFX2	InFlaRx	C5a	Ab
SOBI005	SOBI	C5	Affibody
Name not disclosed (oral)	RaPharma	C5	SM
Zilucoplan extended release	RaPharma	C5	Peptide
CP010	Complement Pharma/Alexion	C6	Ab

Abbreviations (for diseases see Table 2): Ab, antibody; AP, alternative pathway; ASO, antisense oligonucleotide; RNAi, ribonucleic acid interference; CP, classical pathway; LP, lectin pathway; FB, factor B; FD, factor D; FH, factor H; FI, factor I; MASP, mannose-associated serine protease 1; PNS, peripheral nervous system; CNS, central nervous system; MAC, membrane attack complex; FDA, The Food and Drug Administration; EMA, European Medicines Agency; SM, small molecule; IV, intravenous; SC, subcutaneous; IVT, intravitreal; Ph, phase; RoA, route of administration; SoC, standard of care; ULN, upper limit of normal; AQP4, Aquaporin-4.

Table 3. Drugs in current clinical trial. Each line represents a clinical trial and these are shaded according to the phase of development. Only company-sponsored trials are indicated and completed trials are excluded. Red text indicates that a drug has already been approved for treatment of a different indication and is being trialled for a new purpose. For disease abbreviations refer to Table 1. For modality and route of administration please refer to Table 2. HV; healthy volunteer.
* Recently approved by FDA for NMOSD, June 2019

Drug	Phase 1 (or 1/2)	Phase 2	Phase 3
AAVCAGscd59	GA, NCT03144999		
AAVCAGscd59	wAMD, NCT03585556		
ABP 959 (eculizumab biosimilar)	HV, ACTRN12616000509460		
Danicopan (ACH-4471)	C3G/IC-MPGN, NCT03124368 (proof-of-mechanism)		
Danicopan	C3G, NCT03369236		
Danicopan	C3G/IC-MPGN, NCT03459443		
Danicopan	PNH, NCT03181633		
Danicopan	PNH (combination, inadequate response to Eculizumab); NCT03472885		
ACH-5228	HV		
ACH-5448	HV		
AMY-101	Gingivitis, NCT03694444 (Ph 1/2)		
APL-2	PNH, NCT03500549		
APL-2	PNH, NCT03531255		
APL-2	GA, NCT03525600,		
APL-2	GA, NCT03525613		
APL-2	neovascular AMD, NCT03465709 (Ph 1/2)		
APL-2	WAIHA, CAD, NCT03226678		
APL-2	IgAN, LN, MN, C3GN, DDD, NCT03453619		
APL-9	HV		
Avacopan	AAV, NCT02994927		
Avacopan	C3G, NCT03301467		
Avacopan	HS, NCT03852472		
Berinert	Add-on to Standard of Care, refractory AMR, NCT03221842		
Cemdisiran	IgAN, NCT03841448		
Cinryze	Donor pre-treatment in KT; NCT02435732		
Crovalimab (SKY59)	PNH, NCT03157635 (Ph1/2)		
Eculizumab	gMG (pediatric), NCT03759366		
Eculizumab*	Relapsing NMO extension study, NCT02003144		
IFX-1	PG, NCT03971643		
IFX-1	HS, NCT03487276		
IFX-1	AAV: GPA, MPA, NCT03712345 (add on to SoC)		

Abbreviations (for diseases see Table 2): Ab, antibody; AP, alternative pathway; ASO, antisense oligonucleotide; RNAi, ribonucleic acid interference; CP, classical pathway; LP, lectin pathway; FB, factor B; FD, factor D; FH, factor H; FI, factor I; MASP, mannose-associated serine protease 1; PNS, peripheral nervous system; CNS, central nervous system; MAC, membrane attack complex; FDA, The Food and Drug Administration; EMA, European Medicines Agency; SM, small molecule; IV, intravenous; SC, subcutaneous; IVT, intravitreal; Ph, phase; RoA, route of administration; SoC, standard of care; ULN, upper limit of normal; AQP4, Aquaporin-4.

IFX-1	AAV: GPA, MPA, NCT03895801 (steroid replacement)
IONIS-FB-L_{RX}	AMD (GA), NCT03815825
IONIS-FB-L_{RX}	IgAN, NCT04014335
LPN023	IgAN
LPN023	C3G
LNP023	PNH
Mirococept	Ischaemia-reperfusion injury associated with renal transplantation (Registry: ISRCTN49958194)
Narsoplimab (OMS721)	TMA, aHUS, NCT03205995
Narsoplimab	IgAN, NCT03608033
Narsoplimab	LN, MN, C3G, NCT02682407
Narsoplimab	TMA, NCT02222545
Nomacopan (Coversin)	PNH, NCT03588026
Nomacopan	PNH in patients resistant to eculizumab, NCT03427060
Nomacopan	Long Term Safety and Efficacy in PNH & aHUS, NCT03829449
Nomacopan	BP (Europe)
Nomacopan	Ph 1/2, atopic keratoconjunctivitis (AK)
Pozelimab	PNH
Ravulizumab	aHUS (Adults and Adolescents, treatment naive), NCT02949128
Ravulizumab	aHUS (Children and Adolescents), NCT03131219
Ravulizumab	gMG, NCT03920293
Ravulizumab	PNH (Children and Adolescents), NCT03406507
Ruconest	DGF after KT, NCT03791476
Sutimlimab	BP, CAD, wAIHA, NCT02502903
Sutimlimab	CagD (Cardinal study), NCT03347396
Sutimlimab	CagD (Cadenza study), NCT03347422
Tesidolumab	PNH, NCT02534909
Zilucoplan	PNH extension study, NCT03225287
Zilucoplan	gMG, NCT03315130
Zilucoplan	IMNM, NCT04025632
Zilucoplan	Renal disorders
Zimura	STGD1, NCT03364153
Zimura	GA, NCT02686658

Figure 1

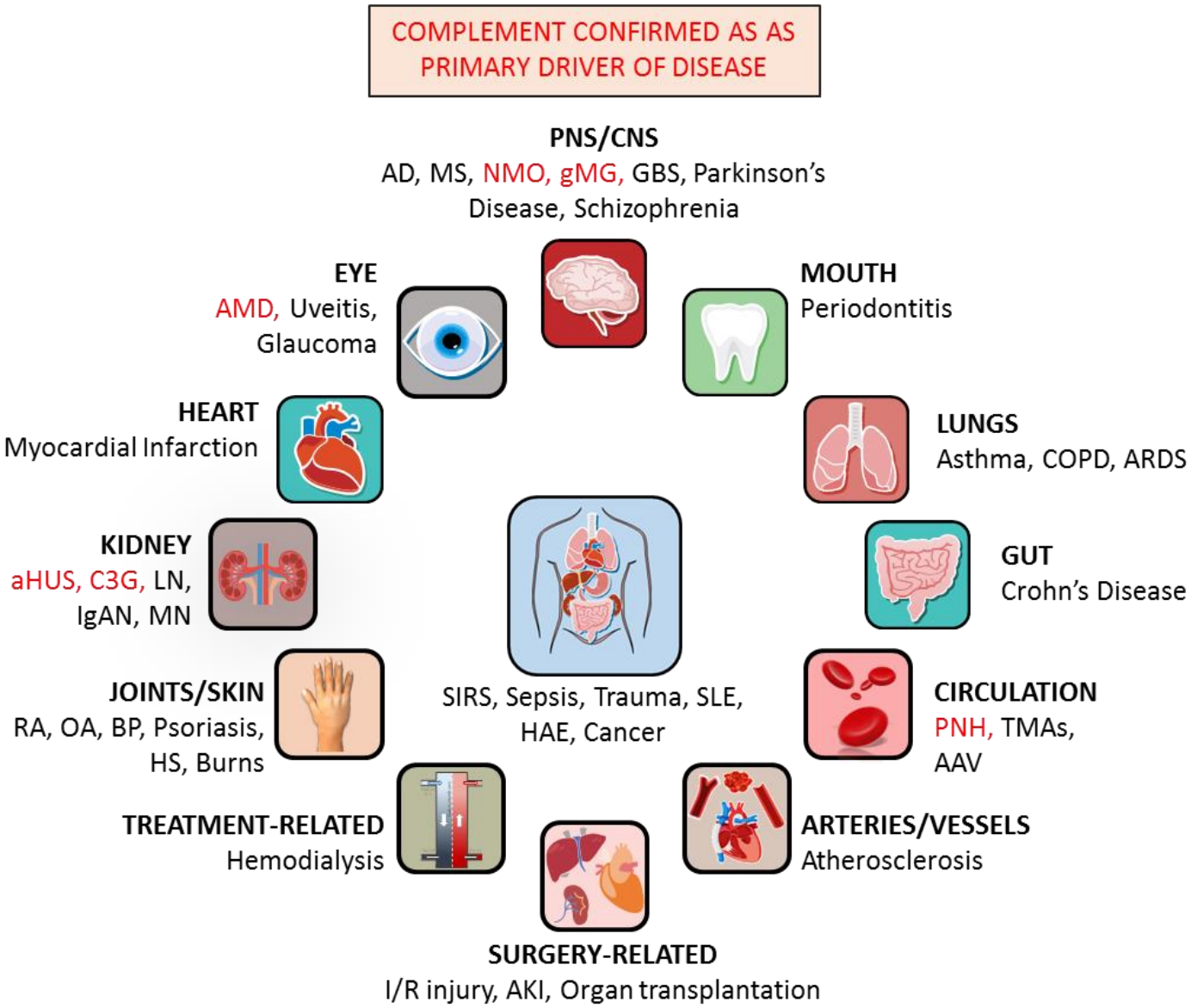

COMPLEMENT CONFIRMED AS AS PRIMARY DRIVER OF DISEASE
PNS/CNS
AD, MS, NMO, gMG, GBS, Parkinson's Disease, Schizophrenia
EYE
AMD, Uveitis, Glaucoma
MOUTH
Periodontitis
HEART
Myocardial Infarction
LUNGS
Asthma, COPD, ARDS
KIDNEY
aHUS, C3G, LN, IgAN, MN
GUT
Crohn's Disease
SIRS, Sepsis, Trauma, SLE, HAE, Cancer
JOINTS/SKIN
RA, OA, BP, Psoriasis, HS, Burns
CIRCULATION
PNH, TMAs, AAV
TREATMENT-RELATED
Hemodialysis
ARTERIES/VESSELS
Atherosclerosis
SURGERY-RELATED
I/R injury, AKI, Organ transplantation

Figure 2

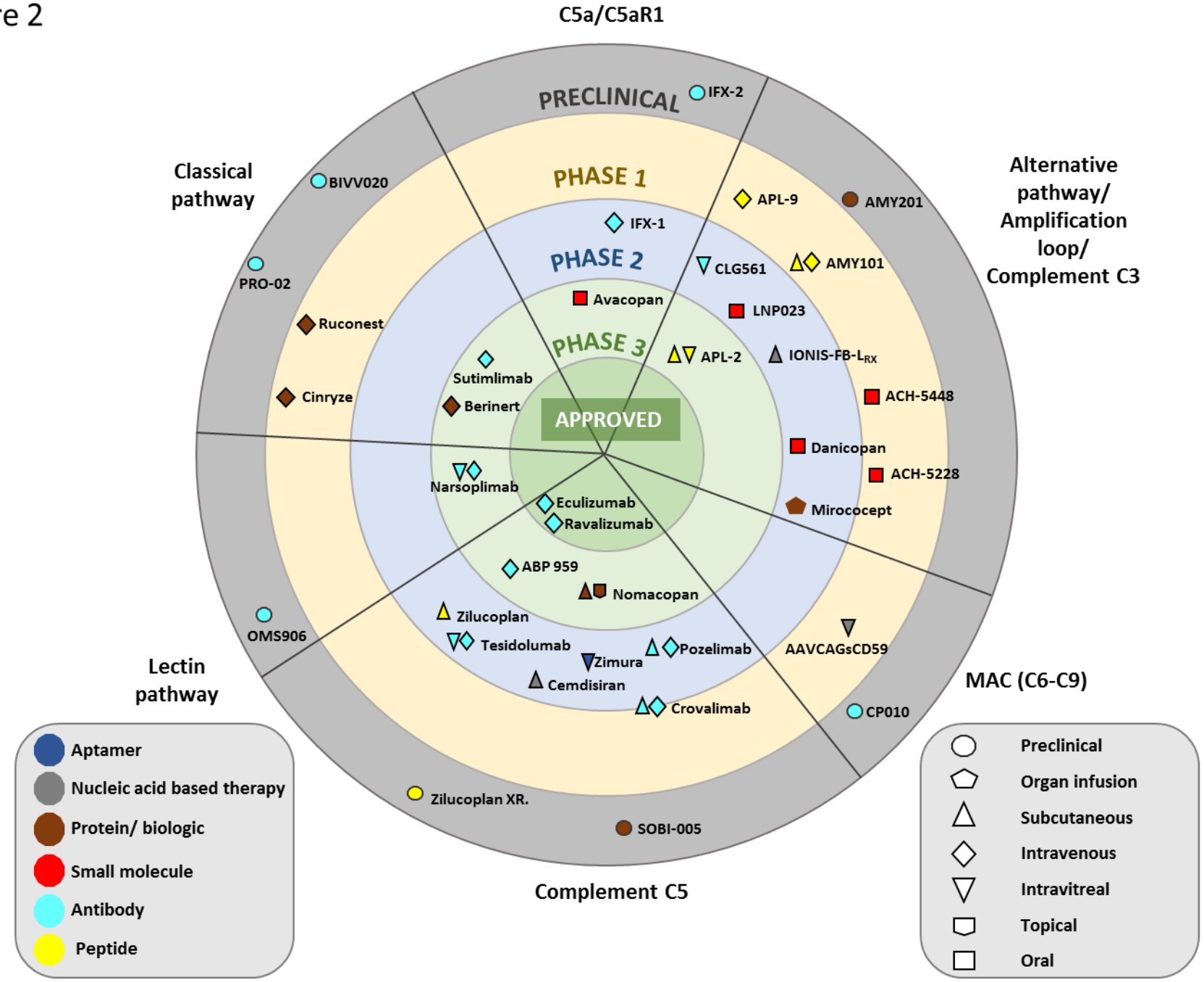
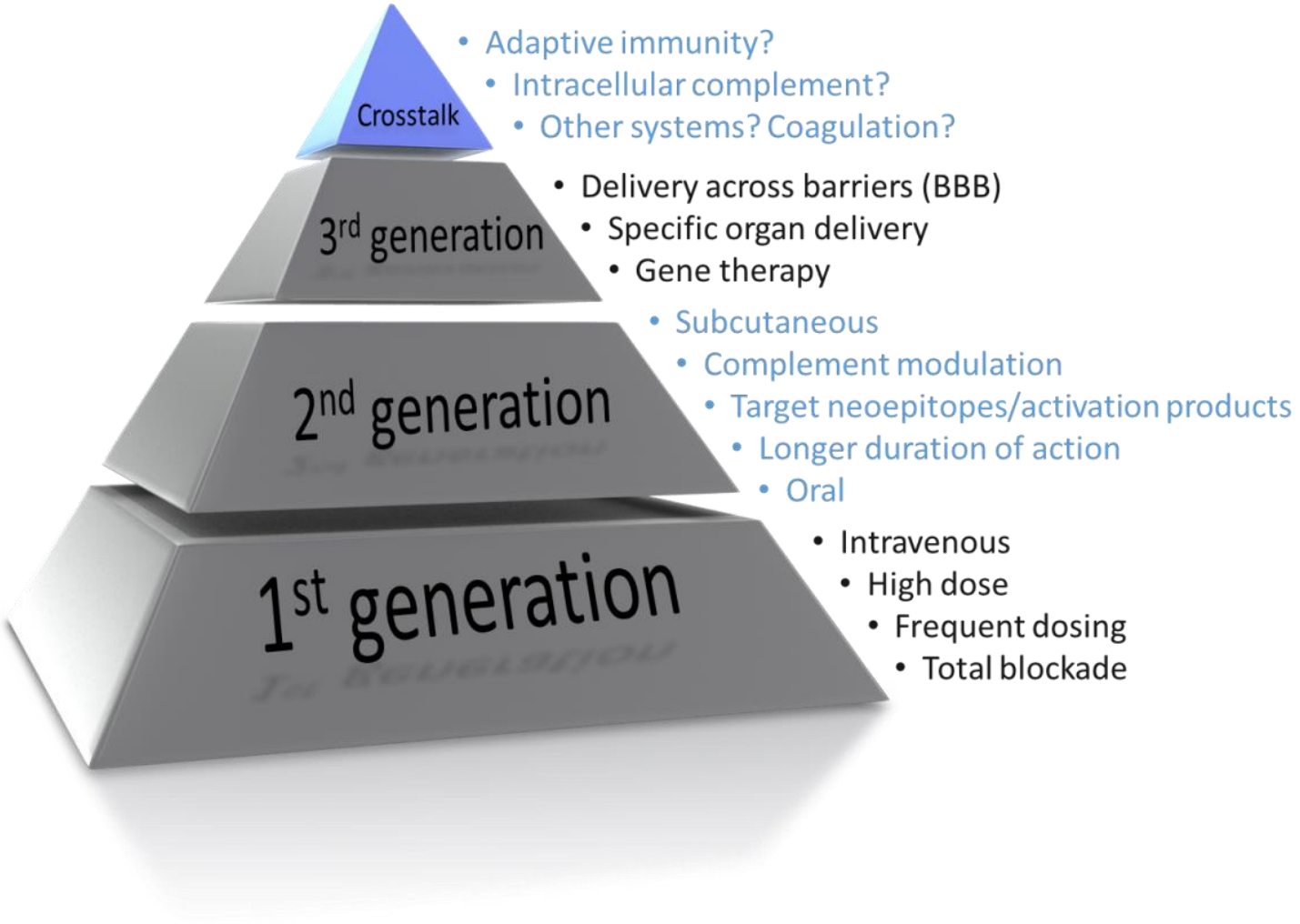

C5a/C5aR1
PRECLINICAL
PHASE 1
PHASE 2
PHASE 3
APPROVED
IFX-2
IFX-1
APL-9
AMY201
CLG561
AMY101
Avacopan
LNP023
APL-2
IONIS-FB-LRX
ACH-5448
Danicopan
ACH-5228
Mirococept
Eculizumab
Ravalizumab
ABP 959
Nomacopan
Pozelimab
Crovalimab
Cemdisiran
Zimura
Tesidolumab
Zilucoplan
Narsoplimab
Sutimlimab
Berinert
Cinryze
Ruconest
PRO-02
BIVV020
OMS906
Zilucoplan XR.
SOBI-005
CP010
AAVCAGsCD59
Classical pathway
Alternative pathway/ Amplification loop/ Complement C3
Lectin pathway
MAC (C6-C9)
Complement C5
Aptamer
Nucleic acid based therapy
Protein/ biologic
Small molecule
Antibody
Peptide
Preclinical
Organ infusion
Subcutaneous
Intravenous
Intravitreal
Topical
Oral

Figure 3


Crosstalk
• Adaptive immunity?
• Intracellular complement?
• Other systems? Coagulation?
3rd generation
• Delivery across barriers (BBB)
• Specific organ delivery
• Gene therapy
2nd generation
• Subcutaneous
• Complement modulation
• Target neoepitopes/activation products
• Longer duration of action
• Oral
1st generation
• Intravenous
• High dose
• Frequent dosing
• Total blockade

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