Commentary

From discovery to approval: A brief history of the compstatin family of complement C3 inhibitors

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A B S T R A C T

The FDA approval of pegcetacoplan (Empaveli), a PEGylated compstatin-based C3 therapeutic, as a new treatment for paroxysmal nocturnal hemoglobinuria (PNH) marks a milestone in the history of complement drug discovery. Almost 15 years after the approval of the first complement-specific drug for PNH, the anti-C5 antibody eculizumab, a novel class of complement inhibitors with a distinct mechanism of action finally enters the clinic. This landmark decision broadens the spectrum of available complement therapeutics, offering patients with unmet clinical needs or insufficient responses to anti-C5 therapy an alternative treatment option with a broad activity profile. Here we present a brief historical account of this newly approved complement drug, consolidating its approval within the long research record of the compstatin family of peptidic C3 inhibitors.

‘This is a proof of the story, so that the deeds of men may not be effaced by time’

Herodotus, Histories

1. A changing ‘landscape’

Complement-targeted drug discovery has evolved hand in hand with our growing appreciation of the complement system’s involvement in human health and disease. An ever-expanding list of human pathologies linked to deregulated or excessive complement activation has incentivized both academic and corporate-led efforts to develop complement therapeutics as new immunomodulatory drugs [1–3]. This endeavor, however, proved to be more challenging than anticipated. The sheer complexity of this innate immune cascade, reflected by multi-pronged interactions with other host defense systems operating both in the intravascular space and in many tissues, attests to the challenging nature of the drug discovery effort [4,5]. Complement’s pervasive involvement in disease pathogenesis has been documented across a spectrum of diverse pathologies, validated by many preclinical proof-of-concept (PoC) studies and further corroborated by human clinical/translational studies [6,7]. These studies have not only illuminated previously elusive roles of complement in human pathophysiology but have also underscored the precept that clinical complement intervention cannot thrive on a “one size fits all” approach. Results from clinical trials, high-resolution patient immunophenotyping and genetic association studies point to the conclusion that therapeutic complement modulation would strongly benefit from a personalized medicine/targeted approach [8]. Ideally, tailored complement therapeutics should target discrete complement effectors and pathways that are integrally involved with disease pathogenesis or clinical exacerbation. The selection of stratified patient groups, the timing of complement intervention and the choice of optimal delivery routes are crucial parameters that may ultimately decide the clinical success of complement therapeutics [2,3].

For almost two decades, the notion of tailored complement intervention has been entertained as a ‘forward-looking’ statement rather than being a reality in clinical practice. The restricted therapeutic arsenal, with eculizumab (Soliris, Alexion) long remaining the sole complement-specific drug, had a strong impact on the clinical landscape regarding complement-related indications and affordability [9]. Soliris, approved in 2007, was the first complement-specific drug to be approved for the treatment of paroxysmal nocturnal haemoglobinuria (PNH), a rare hemolytic disorder [10]. The antibody blocks the cleavage of complement protein C5, thereby preventing the generation of the anaphylatoxins C5a and the assembly of the cytolytic membrane attack complex (MAC; C5b-9). C1 esterase inhibitor (C1-INH), a plasma serine
protease inhibitor with broader target specificity including the comple- 
ment, coagulation and fibrinolytic systems was approved for hered-
itary angioedema (HAE) in 2008 but had already been used in Europe for 
more than 30 years to treat patients with C1 inhibitor deficiency [2,11]. 
The clinical development of Soliris was spearheaded by the discovery of 
the first mouse C5–specific monoclonal antibody by Frei, Lambris and 
Stockinger in the 1980s and its successful application in preclinical 
disease models where C5 blockade was shown to ameliorate inflam-
matory tissue damage [12,13,58]. Since the initial approval of Soliris for 
PNH, the indication range has been expanded to atypical hemolytic 
uremic syndrome (aHUS), neuromyelitis optica (NMO) and refractory 
generalized myasthenia gravis, all representing rare diseases of the renal 
or neurological spectrum [2]. Owing to its unique position, and despite 
targeting only one effector pathway, Soliris has served for many years as 
the defining ‘springboard’ for investigating the potential benefits of 
therapeutic complement modulation. Although the recent launch of 
raulizumab (Ulxomiris, Alexion) introduced a second complement 
drug, this antibody corresponds to a long-acting version of eculizumab 
that shares the same target, i.e., C5, and the same mode of action with 
Soliris [14]. Our clinical experience with complement inhibition has 
therefore been largely restricted to a single mechanistic approach.

2. The approval

By providing a therapeutic intervention distinct from anti-C5 treat-
ment, the approval of pegcetacoplan (Empaveli, Apellis) marks a 
watershed moment in the history of complement therapeutics that could 
change the course of clinical management in many complement-
mediated diseases for which anti-C5 therapy has yielded mixed or 
insufficient responses [15,16]. The clinical introduction of the first C3-
targeted inhibitor not only enables tailored complement modulation in 
diseases driven or exacerbated by C3 dysregulation [2] but also serves as 
an important validation of prolonged C3 inhibition as a treatment 
strategy. For many years, C3-targeted approaches had been scrutinized 
for their potentially compromising impact on immune defense. Such 
safety concerns were based on the well-recognized role of C3 in the 
innate immune response against pathogens and on clinical observations 
with C3-deficient patients [17]. However, arguments regarding the 
protective impact of adaptive immunity or the reversibility of the 
treatment were often not taken into account, and the reservations 
against this approach remained largely based on hypothetical assump-
tions rather than clinical experience. Scientific discussions remained 
focused on this aspect, even after initial clinical trials of C3 inhibitors 
revealed reasonable safety profiles and preclinical studies pointed to a 
redundant or even opposing role of C3 in pathogen surveillance [18]. 
Largely thanks to the experience with pegcetacoplan and other members 
of the compstatin family, we have finally arrived at a more leveled and 
evidence-based safety assessment that places C3 inhibitors, alongside 
anti-C5 agents, in those therapeutic modalities whose risk can be 
managed successfully through careful monitoring and prophylactic 
vaccination against certain encapsulated bacteria. The approval of 
Empaveli reverberates the notion that C3 inhibitors can offer broad 
therapeutic benefit to patients with unmet clinical needs as long as a 
 thorough risk mitigation strategy is in place.

3. The story behind the approval

Corporate-led programs frequently advance through clinical devel-
 opment drug candidates that have originally been discovered and vali-
dated in an academic setting [19]. The case of Empaveli serves as an 
illustrative example of academic-led research that was successfully 
 transferred to the corporate pipeline at an already mature stage. Its 
clinical approval marks the culmination of a rigorous and longstanding 
research and development effort by Prof. John Lambris, a leading 
immunologist who pioneered C3-targeted complement inhibition. In 
fact, Empaveli’s discovery is deeply rooted in the long research record of 
the compstatin family of C3-inhibiting peptides, which was discovered 
and characterized by the Lambris group at the University of Pennsyl-
 vania [20–22]. The key structural determinants of their target selectivity 
and inhibitory mode of action as well as their efficacy in blocking C3 
avtivation in vivo were extensively investigated by the group through 
vital collaborations with an extensive network of international experts 
in various aspects of complement pathobiology and drug discovery. The 
rich history and solid validation of this class of C3 therapeutics spans 
over 25 years and is reflected by an extensive publication record that 
numbers more than 150 papers in peer-reviewed journals. The multi-
disciplinary drug discovery program coordinated by the Lambris 
group and involving more than 130 scientists worldwide received 
generous support from NIH and other international funding agencies 
and has yielded over the years 4 generations of compstatin derivatives 
with discrete molecular and pharmacologic features.

Compstatins comprise a family of structurally related cyclic peptides 
that selectively bind to human and non-human primate C3 and inhibit 
its cleavage by C3 convertases, acting as protein–protein interaction 
inhibitors that block the access of the convertases to their substrate C3 
[22–24]. The parental molecule of this family, a 13 amino acid long-
disulfide-bridged peptide, was discovered in 1996 through phage 
display peptide library screening using C3b as ‘bait’ [25] (Fig. 1). The 
original goal of that screening was to isolate multiple C3-binding pep-
tides that could potentially inhibit C3’s interaction with its known li-
gands. However, this effort resulted in the isolation of only one peptide, 
but it caught attention as its C3 inhibitory potential was better than 
other C3 inhibitory peptides known to that date. Advanced analogs with 
increased inhibitory activity, enhanced target residence and favorable 
pharmacokinetic profiles for systemic administration were selected 
through successive rounds of structure-guided peptide modifications 
and lead optimization. These efforts were propelled by a wealth of 
structural and molecular insights from biochemical assays [26], NMR 
studies [27], in silico modeling [28,29], crystallographic analysis [24] 
and preclinical PoC studies in disease models where compstatins showed 
sustained inhibitory potency and therapeutic efficacy [18,30–37,59] 
(for detailed reviews on the development of compstatin-based drug 
candidates please see: [20–22]). Currently, third- and fourth-generation 
compstatin derivatives with superior solubility, efficacy and/or phar-
macokinetic profiles (e.g., AMY-101, AMY-106) are clinically developed 
by Amyndas Pharmaceuticals for various indications [38,39] (Fig. 1).

4. The discovery of APL-2/pegcetacoplan

Empaveli (pegcetacoplan, APL-2) is a PEGylated C3 therapeutic 
comprising two copies of the second-generation compstatin analog APL-
1/POT-4 bridged by a 40 kDa PEG moiety to improve plasma residence. 
The pharmacologically active moiety of this drug is the second-
generation compstatin analog 4(1MeW)7W (Cp05), which was 
discovered by the Lambris group through targeted peptide modification 
and backbone N-methylation of the compstatin scaffold [40]. This comp-
statin analog was licensed by the University of Pennsylvania to Potentia 
Pharmaceuticals in 2006 and was initially developed as POT-4 for the 
treatment of both the dry and neurovascular (exudative) forms of age-
related macular degeneration (AMD) [41]. Despite advancing to phase 
2 trials in wet AMD in a partnership with Alcon, the compound showed 
limited signs of efficacy likely due to insufficient dosing. After Potentia’s 
clinical development program was transitioned to Apellis Pharmaceut-
cicals, and the drug candidate was renamed to APL-1, a PEGylation 
approach was initiated to enhance the half-life of the peptide drug. In 
APL-2/pegcetacoplan, a PEG linker serves as a molecular bridge to space 
apart two moieties of the APL-1 peptide conjugated to either end of the 
linker. Alongside the now approved use in PNH, Apellis is developing 
and evaluating pegcetacoplan for various indications, including renal, 
nervological and ophthalmic diseases. Of note, the PEGylation of the 
compstatin analog corresponding to APL-1 had already been described in 
a patent filed by Lambris and Katragadda in 2005 [42].
5. PNH: the ‘testbed’ of complement therapeutics

The approval of Empaveli for the treatment of the rare hematological disease PNH signifies a major milestone in the clinical advancement of complement therapeutics. PNH is an archetypal complement-mediated disease in which complement dysregulation on the surface of erythrocytes lacking the GPI-anchored complement regulators CD55 and CD59 is the main driver of pathology, resulting in chronic intravascular hemolysis and increased thrombotic risk [43]. By virtue of its distinct pathophysiology, PNH serves as an ideal clinical ‘testbed’ for developing new complement therapeutics. It also provides a robust platform for benchmarking new complement inhibitors against standard anti-C5 agents, i.e., Soliris and Ultomiris. Persistent C3 fragment opsonization and extravascular C3-mediated clearance of surviving PNH cells was associated with residual anemia in a significant fraction of PNH patients who receive Soliris, thus revealing an unmet medical need not dealt with by the standard treatment [44,45]. The clinical potential of compstatin-based C3 inhibitors in PNH was first demonstrated in 2014 when the third-generation compstatin analog Cp40, alongside its PEGylated derivative, were shown to abrogate both MAC-mediated intravascular hemolysis and C3 fragment opsonization (a surrogate marker of extravascular hemolysis) in PNH erythrocytes [46]. Furthermore, pharmacokinetic studies in cynomolgus monkeys revealed that sustained and target-saturating therapeutic levels of the unmodified C3 inhibitor (Cp40) could be achieved through repeated SQ administration. These findings had important implications by indicating that a peptide-based C3 inhibitor could potentially be delivered as a broadly effective PNH therapeutic that could block both intravascular and extravascular hemolysis, thereby addressing the unmet medical need not dealt with by the standard treatment [44,45]. The clinical potential of compstatin-based C3 inhibitors in PNH was first demonstrated in 2014 when the third-generation compstatin analog Cp40, alongside its PEGylated derivative, were shown to abrogate both MAC-mediated intravascular hemolysis and C3 fragment opsonization (a surrogate marker of extravascular hemolysis) in PNH erythrocytes [46]. Furthermore, pharmacokinetic studies in cynomolgus monkeys revealed that sustained and target-saturating therapeutic levels of the unmodified C3 inhibitor (Cp40) could be achieved through repeated SQ administration. 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6. Outlook

The clinical approval of Empaveli brings the compstatin family of C3 inhibitors to the main stage of clinical complement modulation, alongside anti-C5 agents. It also marks a long-awaited clinical validation of the safety and broader efficacy of C3 inhibitors in life-debilitating diseases such as PNH. The data derived from completed and ongoing clinical trials of C3 inhibitors, such as empaveli or AMY-101, corroborate earlier observations that the systemic delivery of C3 inhibitors is not only feasible but can also adequately saturate the plasma concentration of C3, affording the need for blood transfusions in PNH patients that remained transfusion-dependent under treatment with Soliris. Of note, pegcetacoplan showed superiority over Soliris as it significantly improved hemoglobin levels and key hematologic and clinical markers of disease over a treatment course of 16 weeks.
C3 dysregulation. At the same time, additional inhibitors targeting distinct complement initiators, convertase components or downstream effectors are advancing through late-stage clinical development as treatment options for complement-mediated diseases, bringing tailored complement inhibition and personalized medicine closer to fruition. These anti-complement agents include small-sized orally bioavailable inhibitors of the alternative pathway (FB or FD-targeting agents), classical pathway-specific therapeutics (anti-C1s mAb) and a range of terminal pathway inhibitors (anti-C5a mAb or CSAr1 antagonists) [3,15].

Bringing peg Pegacoplan to the clinic is a great success for Apellis. Yet it also marks the culmination of the long, enduring and prolific scientific journey of John Lambris, into the discovery, optimization and clinical advancement of compstatin-based C3 inhibitors. His scientific perseverance and commitment to developing the next generation of complement therapeutics will surely bear the indelible mark of clinical C3 inhibition. What now becomes mainstream has long been considered too risky or even improbable [3,17]. It is telling that this journey against all odds has been ventured by a scientist who challenges dogmas and thinks ‘outside the box’ and who not only connects different fields but also a strong network of academic, clinical and industrial collaborators. His passion for fostering a broad scientific dialogue that can cross-fertilize new concepts in the complement field drove him to found the Aegean Conferences, a scientist-driven, non-profit educational forum that has organized more than 140 successful meetings over the past 20 years. The seminal insights by John Lambris’ group and his collaborators span the evolutionary history and phylogeny [51], structural biology [52], molecular function [53] and immunological crosstalk of the complement system [1] and led to paradigm shifts in our perception of complement’s role in tumorigenesis and cancer immunity [54], tissue regeneration [55], early embryonic development [56] and the synaptic plasticity and refinement of the brain’s neural circuitry [57]. Such insights were instrumental for the continuous development of the compstatin class of C3 inhibitors. At the same time, compstatin analogs have not only emerged as therapeutic options for tailored complement modulation but serve as valuable tools to answer important research questions about complement’s role in health and disease.

It is our conviction that the landmark approval of Empavali will garner renewed interest into the broader prospects of clinical complement intervention, opening up new avenues of opportunity for therapeutic C3 inhibition in yet unexplored clinical indications.

Declaration of Competing Interest

A.S. is a co-inventor of the compstatin technology, which has been licensed to Potentia/Apellis. D.R. is a co-inventor of complement inhibitors, including third-generation compstatin analogs that have been licensed to Amyndas, and received consulting and/or speakers honoraria from companies involved in the development of complement-targeted therapeutics, including Roche, Sobi, Greenovation, and Alexion.

Acknowledgments

This article is dedicated to the 67th birthday of Prof. John D. Lambris, the discoverer of compstatins, which fittingly coincided with the landmark approval of the first compstatin-based C3 inhibitor Empavali by the US FDA. Due to space limitations, the authors have mostly cited review articles rather than original research publications and apologize for not being able to elaborate on the breadth of transformative work contributed by many experts and collaborators during the development, optimization and preclinical evaluation of compstatin-based C3 therapeutics. The authors also acknowledge the important contributions of many past colleagues, Lambris lab alumni and collaborators that provided valuable insights into the structure, inhibitory activity and binding mode of compstatins over the years and essentially paved the way for the clinical endorsement of compstatins in a wide spectrum of clinical indications. The authors also thank Dr. A. Syfoerwa (National and Kapodistrian University of Athens) for selecting the ancient greek quote from Herodotus’ Histories.

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