

Structural insights into the mechanism of inhibition of C5 activation by avacincaptad pegol, an aptamer approved for the treatment of geographic atrophy secondary to age-related macular degeneration

Christiana Dinah,¹ presenting on behalf of Ganeswara Rao Musada,² Laura Moreno-Leon,² Arina Afanaseva,³ Nicole Lombardi,² Nicolas Lonfat,⁴ Kenichi Mori,³ Sharon Bakalash,⁴ Hemant Khanna²

¹Ophthalmology Department, London North West University Healthcare NHS Trust, Harrow, UK; ²Astellas Pharma Inc., Westborough, MA, USA; ³Astellas Pharma Inc., Tokyo, Japan; ⁴Formerly Astellas Pharma Inc.

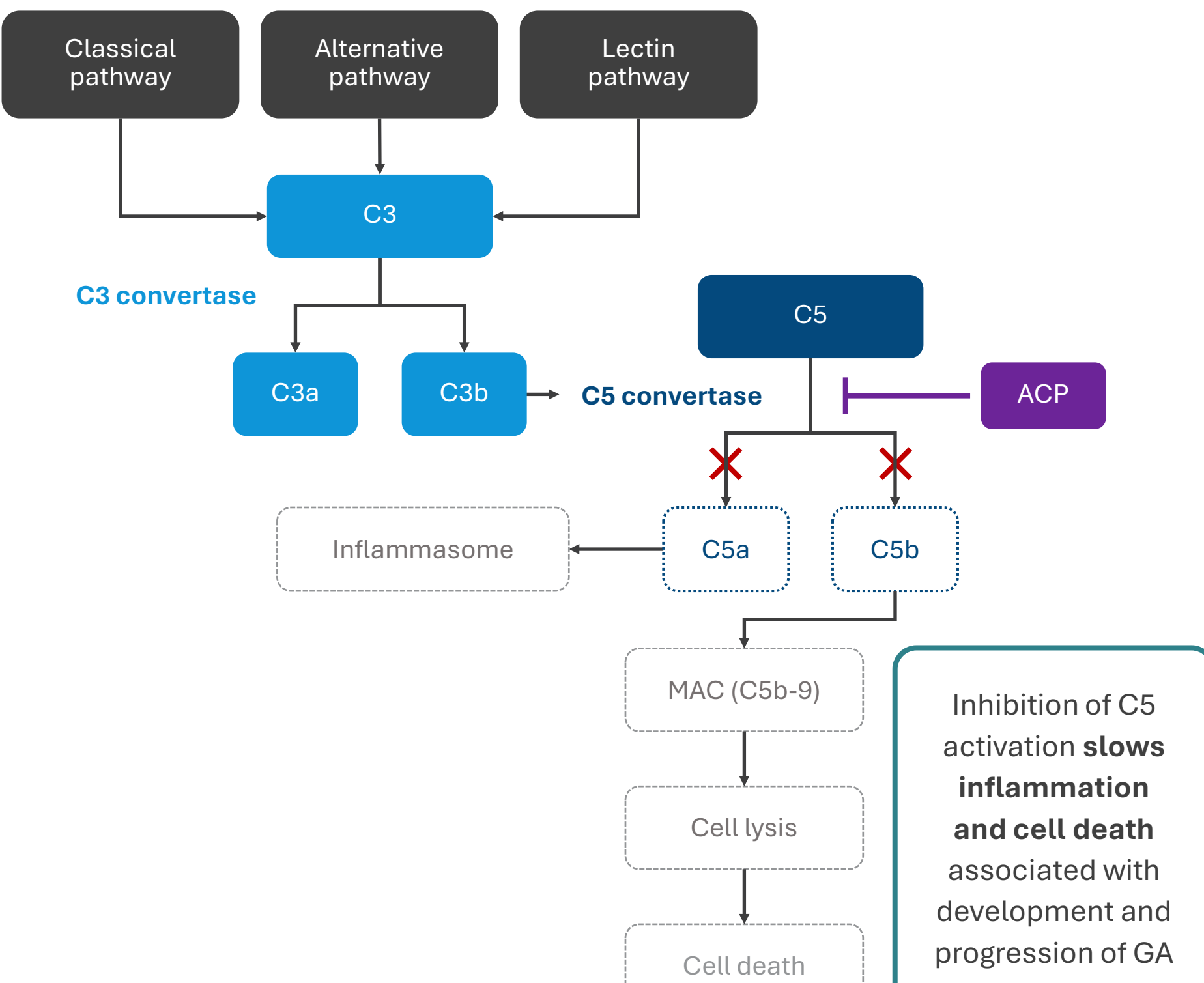
KEY TAKEAWAYS

- ACP selectively inhibits C5 activation, likely through interference with C5 convertase function
- The identified mechanism provides structural rationale for ACP's clinical benefit in GA and may contribute to further development of complement-targeted therapies

INTRODUCTION

- AMD is a leading cause of irreversible vision loss in older adults.¹ GA is an advanced form of AMD characterized by RPE and photoreceptor degeneration and death¹
- Overactivation of the complement system has been implicated in the pathogenesis of GA, contributing to inflammation and cellular damage in the retina²
- ACP is a PEGylated RNA aptamer that specifically binds C5, inhibiting its cleavage and subsequent downstream complement activation (**Figure 1**)^{3,4}

Figure 1. ACP in the complement pathway system



- ACP 2 mg is approved in the USA, Japan, and Australia for the treatment of GA⁴⁻⁶
- Understanding the mechanism of interaction and action of ACP on C5 can help develop novel therapeutics for AMD

OBJECTIVE

- To elucidate the structural mechanism by which ACP inhibits C5 activation, providing a molecular basis for its therapeutic effect in GA

METHODS

- Structural modeling: in silico modeling was used to predict ACP-C5 interaction sites
- Mutagenesis, protein analysis, and gel-shift assay: site-directed mutagenesis generated C5 variants, which were expressed in mammalian cells and purified
 - Human C5 was used to determine the binding affinity of ACP
 - To monitor binding interactions, Cy5-labeled NPA was used to detect binding to both WT and mutant C5 proteins in a gel-shift assay using non-denaturing native gel electrophoresis
 - Fluorescence measurements were performed using a detection wavelength of 680 nm to detect shift in aptamer migration, and Coomassie blue staining was used to detect shift in protein mobility

RESULTS

- ACP-C5 predicted binding domains
 - ACP's 5' and 3' ends that interact with PEG do not engage with C5 directly (**Figure 2A**)
 - In silico modeling identified 3 putative aptamer-interacting residues (Lys882, Lys1578, and Arg1634) on 2 domains (MG7 and C345C) on C5 (**Figure 2B**)
- Gel mobility shift assays confirmed that Arg1634 is not involved in aptamer binding, and that Lys882 and Lys1578 may be peripherally involved in aptamer-C5 interaction (**Figure 3**)
- Simulating convertase binding to C5 indicated that binding of the aptamer to C5 interferes with convertase binding (shown by red line) (**Figure 4**)

Figure 2. ACP-C5 predicted binding domains

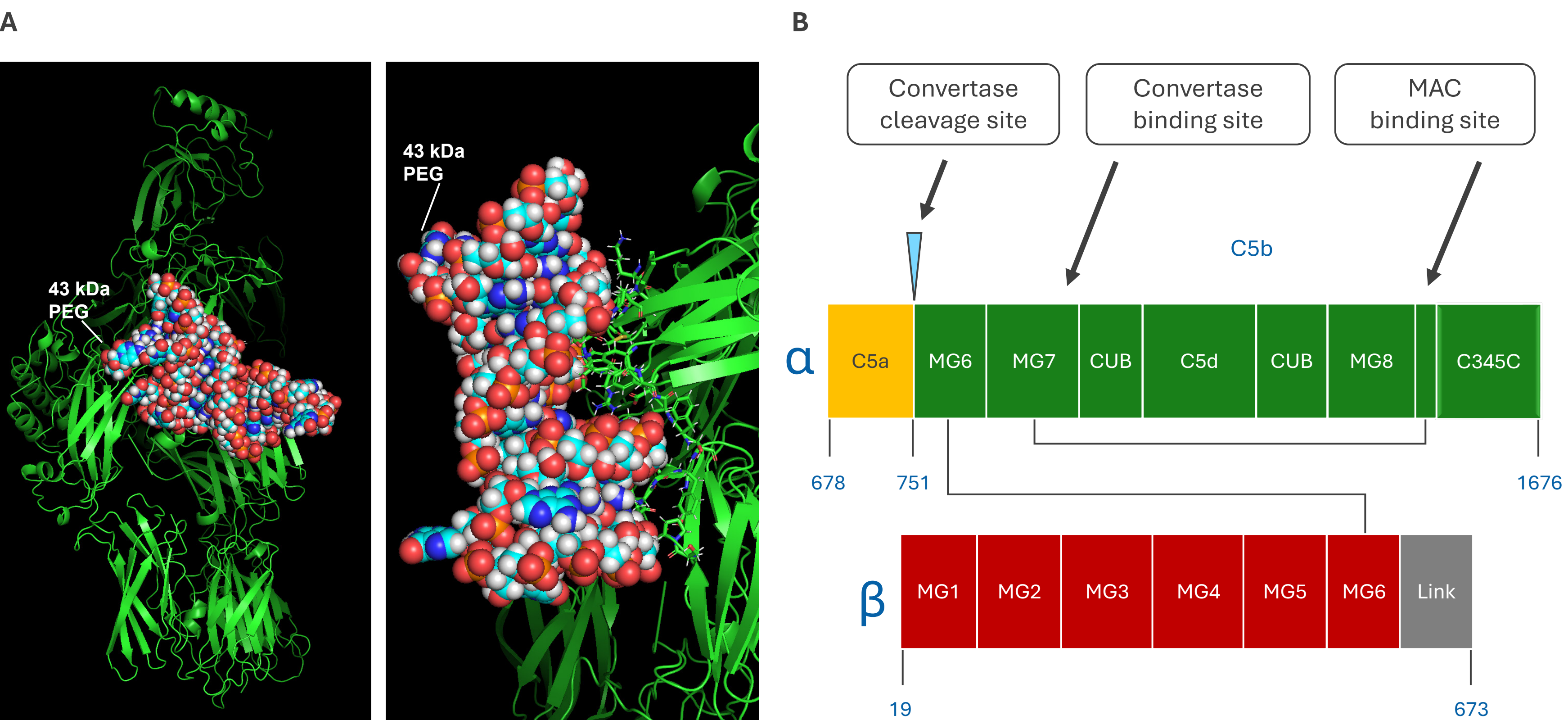


Figure 3. Monitoring aptamer-C5 interactions using (A) fluorescent gel-shift assay and (B) coomassie blue staining

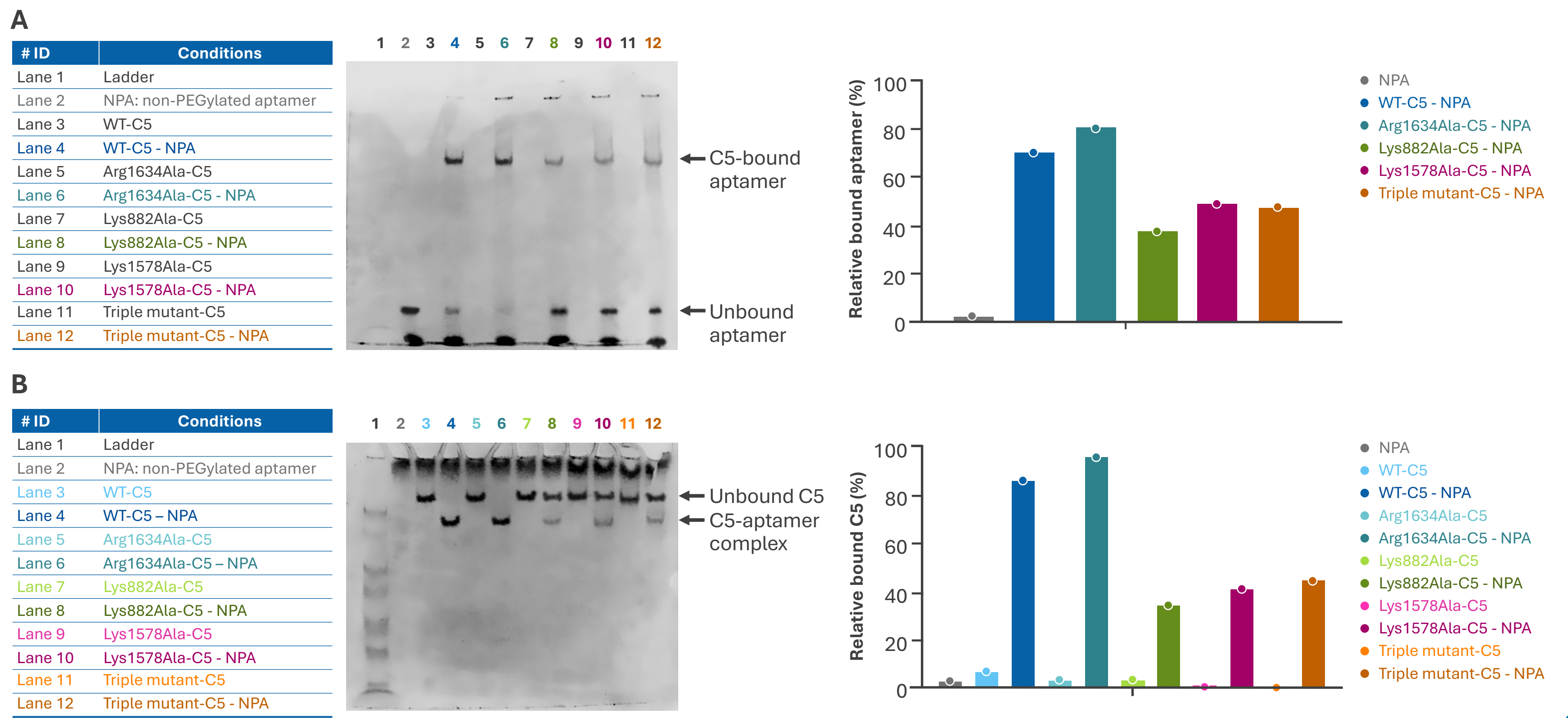
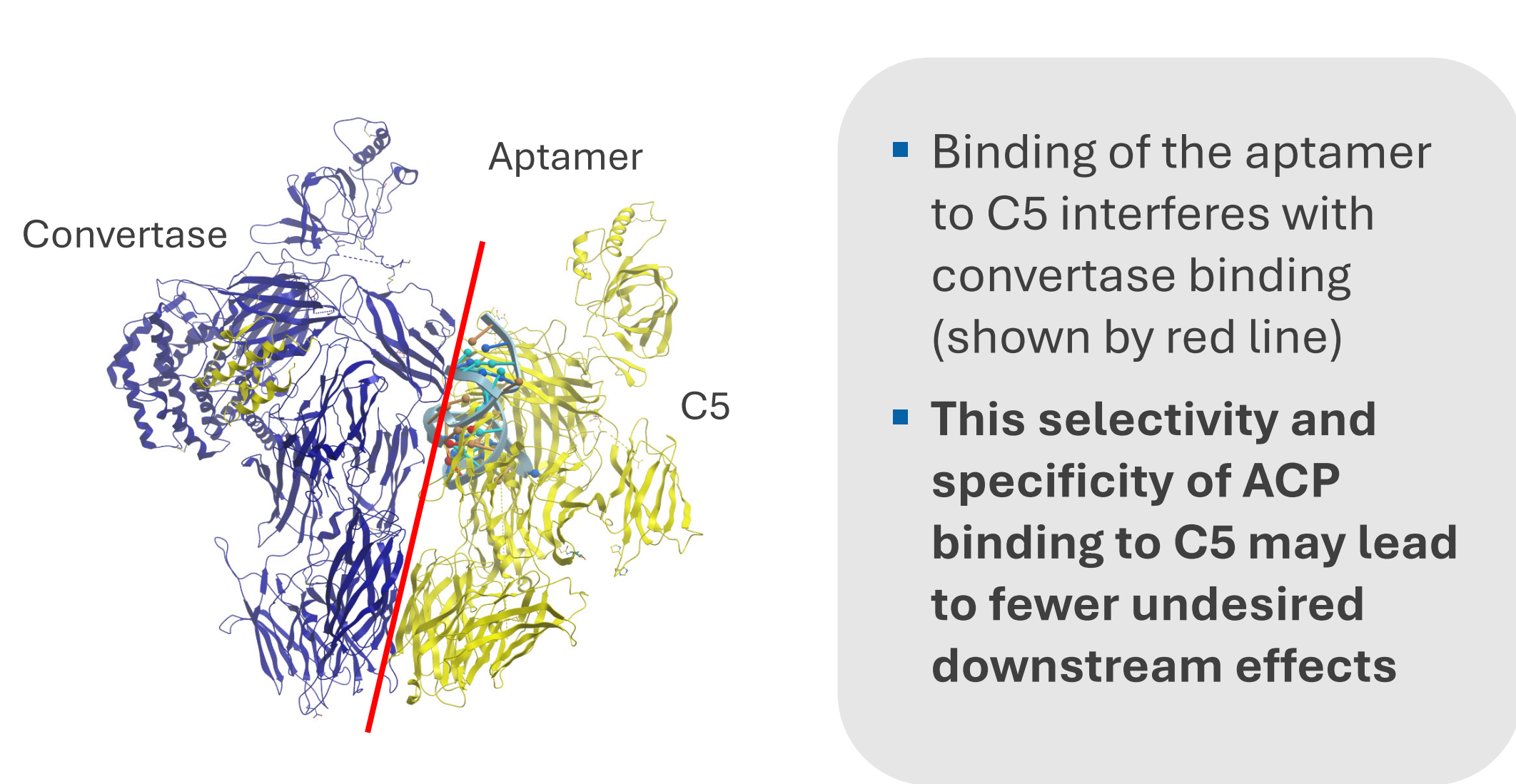


Figure 4. Aptamer binding effect on C5 convertase activation



CONCLUSIONS

- ACP selectively inhibits C5 activation likely by interfering with the C5 convertase interaction or cleavage site access
- ACP binding specifically alters the C5 activation step and may not affect other aspects of the complement pathway
- Additional studies are underway to identify the precise location of ACP-C5 interaction using cryo-electron microscopy

Abbreviations: ACP, avacincaptad pegol; AMD, age-related macular degeneration; GA, geographic atrophy; MAC, membrane attack complex; NPA, non-PEGylated aptamer; PEG, polyethylene glycol; RPE, retinal pigment epithelium; WT, wild-type.

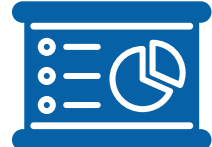
References: 1. Guymer RH, Campbell TG. *Lancet*. 2023;401(10386):1459–1472. 2. Desai D, Dugel PU. *Eye (Lond)*. 2022;36(2):294–302. 3. Danzig CJ, et al. *Immunotherapy*. 2024;16(12):779–790. 4. Izervay Prescribing Information. US Food and Drug Administration; 2025. Accessed October 7, 2025. Available from: <https://www.izervay.com/pi>. 5. Astellas Pharma Inc. Astellas Receives Conditional Approval for IZERVAY, making it the first and only approved treatment for the suppression of geographic atrophy growth in Japan. Published September 19, 2025. Accessed January 16, 2026. 6. Astellas Pharma Australia Pty Ltd. IZERVAY Australian product information; 2025.

Disclosures: Christiana Dinah reports grant support from Apellis; consultant for Apellis, Boehringer Ingelheim, Johnson & Johnson, and Roche; speaker's bureau for Apellis, Boehringer Ingelheim, and Roche; meeting support for Apellis, Boehringer Ingelheim, and Roche; Data Safety Monitoring Board or Advisory Board for Apellis, Boehringer Ingelheim, and Roche. Ganeswara Rao Musada, Laura Moreno-Leon, Arina Afanaseva, Nicole Lombardi, and Hemant Khanna are employees of Astellas Pharma Inc. Nicolas Lonfat was an employee of Astellas Pharma Inc. at the time the study was conducted. Kenichi Mori is an employee and stockholder of Astellas Pharma Inc. Sharon Bakalash was an employee of Astellas Pharma Inc. at the time the study was conducted; is a board member of OIS as well as a consultant for MicroCures.

Funding: This study was funded by Astellas Pharma Inc. Medical writing and editorial support were provided by Samantha Pluta, PharmD, and Cara Farrell of Envision Pharma Group Inc. (CT, USA) and funded by the study sponsor.



Please scan the QR code for:



PDF of Poster

Materials (including a PDF of this presentation) obtained via QR code are for personal use only and not for reproduction.