CD46 is a potent complement cofactor as part of a clinical strategy for Geographic Atrophy

Ciulla Thomas[1]; Vaux Laura[1], Warner Emily[1], Benwell Chris[1], Widdowson Peter[1], Osborne Andrew[1], Binley Katie[1]

[1] Ikarovec Ltd, The NRP Innovation Centre, Norwich, United Kingdom, NR4 7GJ. | info@ikarovec.com

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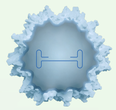
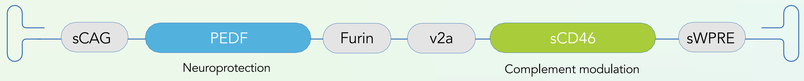
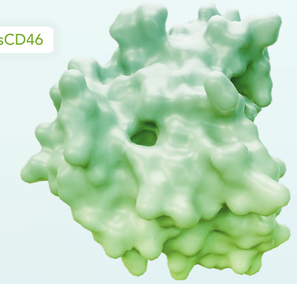
Modulation of the complement pathway is a validated clinical strategy for the treatment of geographic atrophy. CD46 is a key inhibitory regulator of both the alternative and classical cascades and is significantly reduced in GA early in disease, suggesting a replacement therapy rationale (Vogt, 2011; Ebrahimi, 2013). CD46 acts catalytically with Factor I, to inactivate C3b and C4b with more potential efficiency than stoichiometric inhibitors, to prevent excessive membrane attack complex (MAC) formation and subsequent cell lysis. We have assessed soluble CD46 activity across multiple assays to demonstrate its therapeutic potential.

1 IKAR-001: A clinic ready dual-pathway AAV for GA

AAV8 combining PEDF neuroprotection and sCD46 complement modulation in a single vector







2 CD46 activity within the complement cascade

Catalytic cofactor for CFI: inactivates both C3b (alternative) and C4b (classical) upstream of MAC

2a Classical Pathway

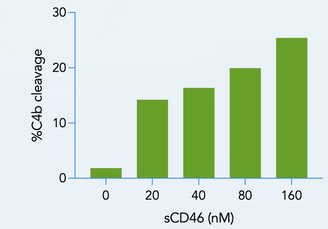
C4b is generated at the antigen-antibody surface

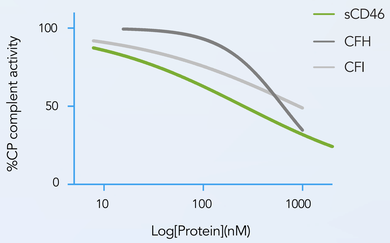
2b Alternative Pathway

C3b is generated at foreign surfaces or by tickover in the fluid-phase

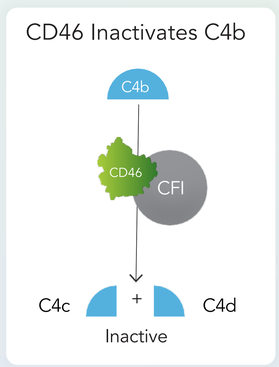
2a Classical Pathway inhibition data

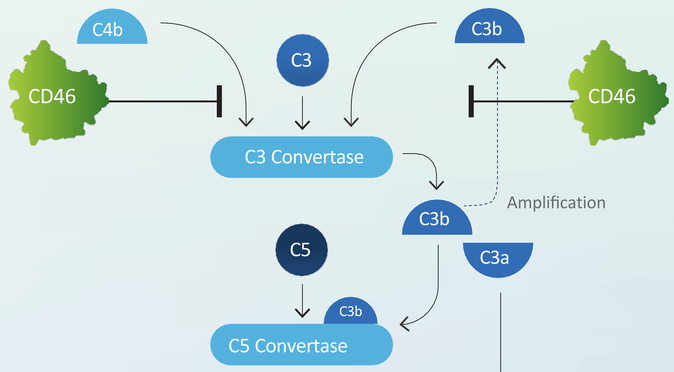
sCD46 provides superior modulation of CP activity, combining higher potency and greater maximal inhibition.

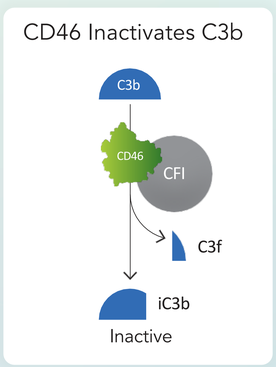




CP - CD46 > CFH > CFI

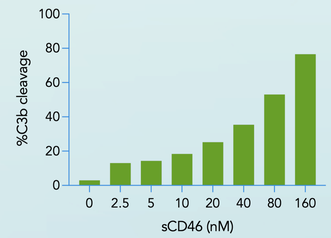


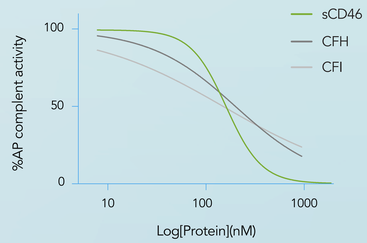




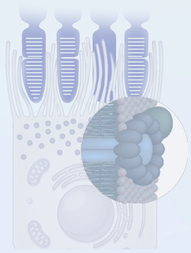
2b Alternative Pathway inhibition data

sCD46 provides superior modulation of AP activity, delivering complete pathway inhibition with greater potency than comparator regulators.





AP - sCD46 ≈ CFI > CFH



C5b C5a

Pro-inflammatory factors

2c Retinal Cell Death

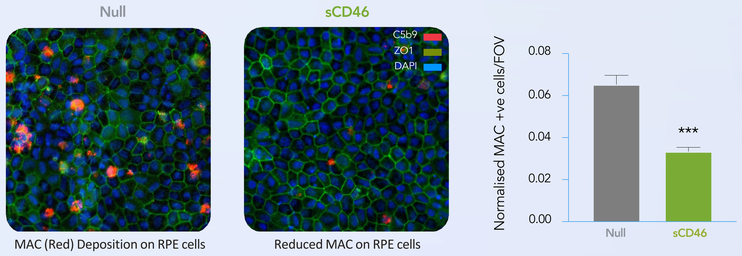
MAC formation leads to Cell Death

Inflammation

Immune cell recruitment

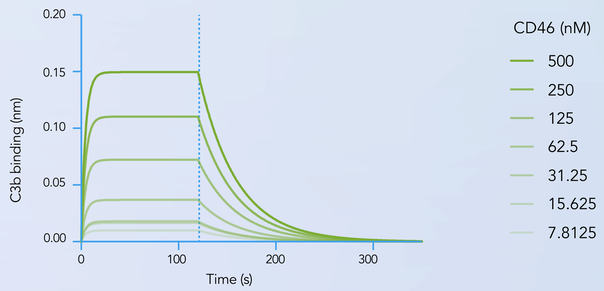
2c Confirms sCD46 activity in human iPSC-RPE, the cells lost in GA

Translational human-cell validation



3 C3b binding to human sCD46

Direct, dose-dependent C3b binding with slow off-rate, consistent with catalytic cofactor function



4 Summary

sCD46: a catalytic, dual-pathway complement regulator with fit-for-purpose GA pharmacology

- sCD46 inhibits both the classical and alternative complement pathways.
- sCD46 is a catalytic cofactor for CFI that functions in the nM range with more potential efficacy than stoichiometric inhibitors to prevent MAC formation.
- Inactivation of both C3b and C4b will reduce anaphylatoxins (C3a and C5a) thus attenuating inflammatory signalling.
- Solubilised sCD46 is potent at reducing terminal complement activity on target RPE cells.

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