158 Tick-derived Polypeptide Complement C5 Inhibitor

Asset Overview

Product Type	Polypeptide isolated from tick saliva
Indication	Diseases associated with uncontrolled complement activation (PNH & aHUS)
Current Stage	Hit generation
Target(MoA)	Direct steric blocking of the docking of C5 onto the C5-convertase
Brief Description	• The complement system is a crucial part of innate immune defenses against invading pathogens • Inhibiting activation of C5 has shown great therapeutic benefit in complement-driven inflammatory diseases, such as atypical haemolytic uremic syndrome (aHUS) and paroxysmal nocturnal hemoglobinuria (PNH) and has potential in the treatment of various human diseases • The novel polypeptide isolated from *Rhipicephalus pulchellus* tick saliva is around 90 residues long, is readily soluble and is chemically and proteolytically stable • It shows a novel mechanism of C5 inhibition by analysis of the binding interface
Organization	University of Oxford

Differentiation

□ **Potential to show the efficacy in eculizumab-resistant patients (Clinical pipelins)**

- Alexion Pharmaceuticals' Anti-C5 antibody, eculizumab (Soliris®): approved in March 2007, sales US$2.6bn in 2015, unmedical needs – cost & need for IV administration at 2-weeks intervals
- Akari Therapeutics' Coversin (*Ornithodoros moubata* tick protein): phase III, SC injection & once-daily self-administration possible, positive preliminary results in an ongoing clinical trial investigating its use in the treatment of PNH in eculizumab-resistant patients
- RNAi Aln-CC5
- 2 anti-C5 minibodies (Mubodina and Ergidina)
- Apellis Pharmaceuticals' APL-2, C3 inhibitor: phase III, directly comparison with Soliris, medical differentiation in treating anemia and reducing transfusion dependency

□ **Novel mechanism of C5 inhibition**

- By identifying the specific binding site, it binds C5 though a novel inhibitory binding site
- Although Coversin binds to C5 in a different location than eculizumab, data so far indicate Coversin acts on C5 in the same way

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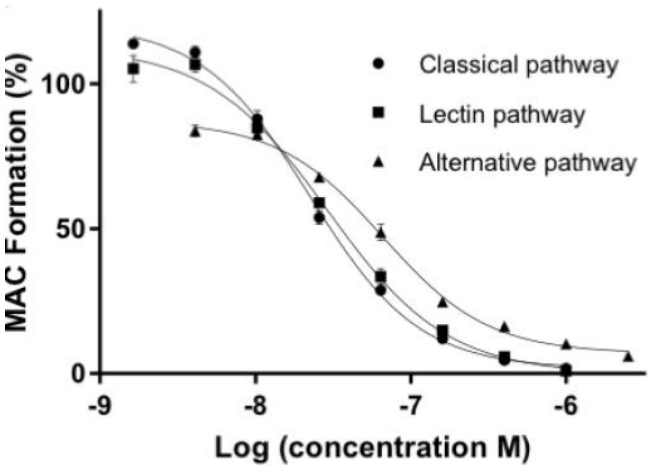
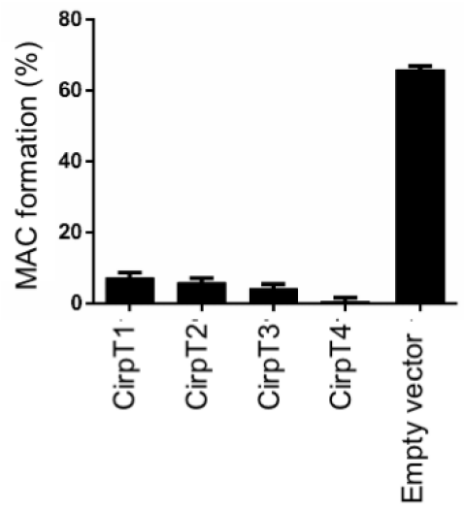
Key Data

CirpTs inhibit complement activation

Complement inhibition assays for CirpT:
shown to inhibit MAC assembly regardless of the initiation pathway of complement

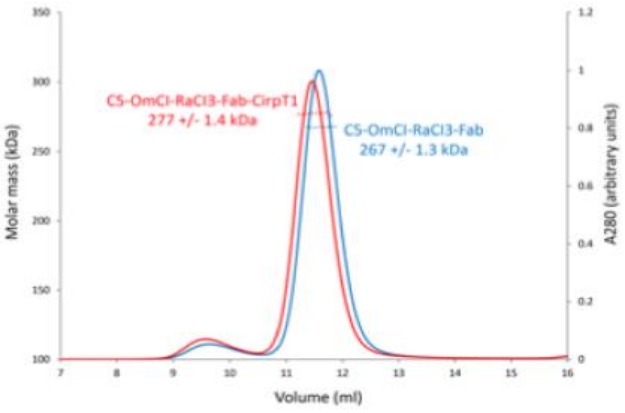


Alternative pathway assay for 4 distinct clusters (CirpT1-4)



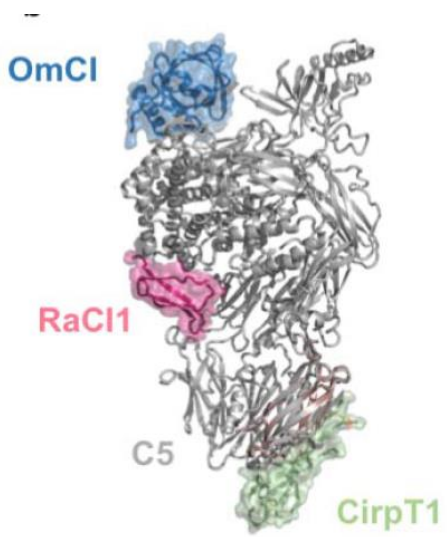
(tested for their ability to inhibit MAC deposition in a standard complement activation assay using human serum - commercial Wieslab assay)

CirpT1 binds C5 through a novel inhibitory binding site



SEC-MALS traces of purified C5 complexed with the inhibitory molecules OmCI, RaCI3, CirpT1 and the Fab fragment Of Eculizumab. Binding of CirpT1 does not compete with any of the other inhibitory molecules, revealing a novel mechanism of inhibition.

Crystal structure of the C5_MG4-CirpT1 complex at 2.7 Å



OmCI: Coversin, RaCI1: tick protein, Fab: eculizumab Fab-gragment

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Intellectual Property

Patent No.	PCT-GB2018-052331
Application Date	2018.08.16
Status	Application Pending
Country	

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