Invariant surface glycoprotein 65 of *Trypanosoma brucei* is a complement C3 receptor important for virulence

Alexander D. Cook[2,†], Olivia J. S. Macleod[1,†], Mandy Crow[1], Helena Webb[1], Roisin Burns[1], Maria Redpath[1], Stefanie Seisenberger[1], Camilla E Trevor[1], Lori Peacock[3], Angela Schwede[1], Nicola Kimblin[1], Amanda F. Francisco[4], Julia Pepperl[1], Steve Rust[5], Paul Voorheis[6], Wendy Gibson[3], Martin C. Taylor[4], Matthew K. Higgins[2,*] and Mark Carrington[1,*]

† These authors made equal contributions

[1]Department of Biochemistry, University of Cambridge, Tennis Court Road, Cambridge CB2 1QW, UK.
[2]Department of Biochemistry, University of Oxford, South Parks Road, Oxford OX1 3QU, UK.
[3]Bristol Veterinary School and School of Biological Sciences, University of Bristol, Bristol, UK.
[4]Faculty of Infectious and Tropical diseases, London School of Hygiene and Tropical Medicine, London, WC1E 7HT, UK.
[5]Antibody Discovery and Protein Engineering, Biopharmaceuticals R&D, AstraZeneca, Cambridge UK.
[6]School of Biochemistry and Immunology, Trinity Biomedical Sciences Institute, Trinity College Dublin, Dublin 2, Ireland.

African Trypanosomes replicate in the blood of mammalian hosts yet are completely exposed to the adaptive and innate immune systems. Despite this, Trypanosomes can sustain long-term infections - how can this parasite survive constant host immune-surveillance? Trypanosomes evade the adaptive immune response through antigenic variation of a surface coat consisting of a dense layer of variable surface glycoprotein. However, very little is known about how they negate the innate system, including the blood circulating complement system. We have discovered that an invariant surface glycoprotein, ISG65, is a receptor for Complement Component 3 (C3). We show how ISG65 binds to the thioester domain of C3b. We also show that knockout of the ISG65 locus greatly decreases the pathogenicity of trypanosomes in a mouse model. Deposition of C3b on pathogen surfaces is a central point in activation of the complement system and C3b has been observed on trypanosome surfaces. Our findings therefore suggest that trypanosomes have a C3 receptor distributed across their surfaces that greatly decreases their susceptibility to complement-mediated killing.