Name	MICHAEL J BLACKMAN
Position	Senior Group Leader
Year joined *(Crick or founder institute)*	1988

Career History

1981-1985: Research Officer, University of Warwick
1985-1988: Research Officer, MRC Laboratories, The Gambia, West Africa
1988-1991: PhD in Biochemistry, MRC National Institute for Medical Research, London
1991-1993: Postdoctoral Fellow, MRC National Institute for Medical Research, London
1993-2000: Career Track Scientist, MRC National Institute for Medical Research, London

Major Awards, Honours and Prizes

2013: Professor of Molecular Parasitology, London School of Hygiene and Tropical Medicine, London UK

Membership of external committees, editorial boards, review panels, SABs etc

Editorial Boards:
2008-present: Academic Editor, *PLoS Pathogens*

Review Panels and SABS etc:
2017-2019: Member, Wellcome Trust Pathogen Biology and Disease Transmission Expert Review Group (ERG)
2017–present: Scientific Advisory Board, University of Dundee Wellcome Trust Centre for Anti-Infectives Research (CAIR)

Lab Name	***Malaria Biochemistry Laboratory***

Research programme and achievements

Malaria is a devastating disease that impacts the lives of over half of the world's population, causing around 228 million clinical cases and over 400,000 deaths in 2018, mostly in children below the age of five. As a result, malaria is a significant contributor to poverty across much of the developing world and remains a significant threat to travellers. The disease is caused by a mosquito-transmitted protozoan parasite which replicates asexually within circulating red blood cells. Each round of intracellular replication culminates in explosive rupture of the host cell and release (egress) of a new wave of invasive merozoites which rapidly bind to and invade fresh red cells. Increasing parasite levels lead to all the clinical manifestations of malaria, including fever, anaemia, hypoglycaemia, acidosis, respiratory distress, and – in the most severe cases – coma and death. Clinical malaria is a medical emergency and can often be fatal even with access to the best medical intervention. There is no widely available malaria vaccine, and widespread resistance to most antimalarial drugs has led to a pressing need to improve our understanding of parasite biology. Malaria parasites are evolutionarily divergent from model eukaryotes (such as yeast), requiring specialised and often novel approaches to dissecting their cell biology and biochemistry. As an example of this, the parasite replicates by schizogony, in which several rounds of nuclear division first generate a multinucleated syncytium (a schizont), followed by a form of cytokinesis called budding that produces daughter merozoites. The timing of egress must therefore be tightly controlled in order to prevent premature release of non-invasive schizonts.

Our research focuses primarily on the molecular mechanisms by which *Plasmodium falciparum*, the agent of the most dangerous form of malaria, enters and exits its host red blood cell. We have identified and characterised several parasite enzymes with key roles in invasion or egress. These include a cGMP-dependent protein kinase called PKG, which in coordination with a complex cyclic nucleotide signalling pathway triggers egress by activating a parasite subtilisin-like protease called SUB1 which is discharged into the parasitophorous vacuole in which the parasite replicates.

There, SUB1 proteolytically modifies the parasite surface to 'prime' it for egress, and also activates a family of papain-like proteins called the SERA proteins that mediate regulatory roles in egress and that precisely cleave and disrupt the host red cell cytoskeleton. Following egress, a further parasite protease called SUB2 sheds proteins from the merozoite surface to enable invasion of a new red cell and resealing of its membrane. We have led advances in understanding the regulation and molecular functions of these essential enzymes, as well as the role of modification of their various substrates, which include several proteins essential for egress and invasion. We have also developed and applied conditional genetic tools that have revolutionised our capacity to dissect malarial gene function. We are working to translate the outcomes of our research into health benefits by seeking drug-like inhibitors of the enzymes and other parasite molecules involved in egress and invasion, and promoting their development as antimalarial drugs.

Research outputs

Patel A[+], Perrin AJ[+], Flynn HR, Bisson C, Withers-Martinez C, Treeck M, Flueck C, Nicastro G, Martin SR, Ramos A, Gilberger TW, Snijders AP and Blackman MJ*, Baker DA*. (2019) *Cyclic AMP signalling controls key components of malaria parasite host cell invasion machinery*. PLoS Biology 17(5):e3000264.
DOI: 10.1371/journal.pbio.3000264

This work demonstrated that the cyclic nucleotide cAMP, through its activation of parasite protein kinase A (PKA) controls host cell invasion by malaria merozoites, but plays no role in the regulation of egress, which is regulated by cGMP. Both production of cAMP and activity of PKA are critical for erythrocyte invasion. The study identified and quantified numerous sites, phosphorylation of which are dependent on cAMP signalling, and provided mechanistic insight as to how cAMP-dependent phosphorylation of the cytoplasmic domain of the essential invasion adhesin apical membrane antigen 1 (AMA1) regulates erythrocyte invasion.

Thomas JA[+], Tan MSY[+], Bisson C, Borg A, Umrekar TR, Hackett F, Hale VL, Vizcay-Barrena G, Fleck RA, Snijders AP, Saibil HR and Blackman MJ. (2018) ***A protease cascade regulates release of the human malaria parasite Plasmodium falciparum from host red blood cells*****. Nature Microbiology 3:447-455. DOI:10.1038/s41564-018-0111-0**
This study showed that egress involves an enzyme cascade in which the serine protease SUB1 activates a second, cysteine protease called SERA6, enabling SERA6 to rapidly and precisely cleave the major red cell cytoskeletal protein β-spectrin and dismantle the cytoskeleton. Provides the first plausible model to explain how the parasite accomplishes timely rupture of its host cell membrane.

Perrin AJ, Collins CR, Russell MRG, Collinson LM, Baker DA and Blackman MJ. (2018) ***The Actinomyosin Motor Drives Malaria Parasite Red Blood Cell Invasion but Not Egress*****. MBio 9(4):e00905-18. DOI: 10.1128/mBio.00905-18**
This study showed that, unlike in the related parasite *Toxoplasma gondii*, egress of *Plasmodium falciparum* merozoites from host erythrocytes does not require actinomyosin-driven motility, placing further emphasis on the protease pathway triggered by cGMP-signalling. In contrast, the *Plasmodium* actinomyosin motor complex is essential for erythrocyte invasion.

Collins CR, Hackett F, Atid J, Tan MSY and Blackman MJ. (2017) ***The Plasmodium falciparum pseudoprotease SERA5 regulates the kinetics and efficiency of malaria parasite egress from host erythrocytes*****. PLoS Pathogens 13:e1006453. DOI: 10.1371/journal.ppat.1006453**
We showed that the most abundant protein in the parasite vacuole, SERA5, is a 'negative regulator' of egress, controlling the speed of the pathway that leads to malarial egress. Loss of SERA5 leads to accelerated but defective egress and reduced parasite replication rates. This work increased understanding of the molecular mechanisms underlying egress and showed that efficient egress requires precise control of the timing of membrane rupture.

Das S, Hertrich N, Perrin AJ, Withers-Martinez C, Collins CR, Jones ML, Watermeyer JM, Fobes ET, Martin SR, Saibil HR, Wright GJ, Treeck M, Epp C and Blackman MJ. (2015) ***Processing of Plasmodium falciparum Merozoite Surface Protein MSP1 Activates a Spectrin-Binding Function Enabling Parasite Egress from RBCs*****. Cell Host & Microbe 18:433-44. DOI: https://doi.org/10.1016/j.chom.2015.09.007**
We demonstrated that proteolytic processing by SUB1 of the most abundant merozoite surface protein, MSP1, is important for parasite viability and activates its capacity to bind spectrin, a molecular scaffold protein that is the major component of the host erythrocyte cytoskeleton. Merozoites lacking surface-bound MSP1 display a severe egress defect.